ISSN 0003-2999
Volume 69, Number 1, July 1989

Anesthesia and Analgesia

31

CALICUT UNIVERSITY
CENTRAL LIBRARY

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

P, 24,561

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

Cule - H02992 - 31 - P024561

Anesthesia and Analgesia

Journal of International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-113

Editorial Board

Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada
Phillip O. Bridenbaugh, MD, Cincinnati, Ohio
Mieczyslaw Finster, MD, New York, New York
Thomas J. Gal, MD, Charlottesville, Virginia
Paul R. Hickey, MD, Boston, Massachusetts
Edward D. Miller, Jr, MD, New York, New York
Walter S. Nimmo, MD, BSC, FRCP, FFARCS, Sheffield, United Kingdom
Nathan L. Pace, MD, Salt Lake City, Utah
Richard J. Palahniuk, MD, Minneapolis, Minnesota
Ronald G. Pearl, MD, PhD, Stanford, California
Donald S. Prough, MD, Winston-Salem, North Carolina
Joseph G. Reves, MD, Durham, North Carolina
John J. Savarese, MD, New York, New York
John H. Tinker, MD, Iowa City, Iowa
Barbara E. Waud, MD, Worcester, Massachusetts

Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 655 Avenue of the Americas, New York, NY 10010, prices on request.

This journal is printed on acid free paper.

The International Anesthesia Research Society is a nonprofit, scientific, an educational corporation in the state of Ohio. Members of the Board of Trustee of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Martin, MD Edward D. Miller, Jr, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K C. Wong, MD, PhD. Emeritus Trustees are: Paul R. Dumke, MD, Morris J Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS i two indexed volumes per year by Elsevier Science Publishing Co, Inc, 65 Avenue of the Americas, New York, NY 10010. Printed in USA. © 198 International Anesthesia Research Society. Second class postage paid a New York, NY and at additional offices.

Subscription information for 1989 applying to IARS members: USA an possessions, $70.00 per year, in all other countries $89.00. Membership i available to individuals with doctorate degrees in medicine, osteopathy dentistry, veterinary medicine, or other disciplines who are engaged i active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited b anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant) EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS membe subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Cente Road, Cleveland, Ohio 44122.

Subscription information for 1989 applying to non-IARS members: Institutions, $112.00; nonmember individuals, $85.00. Outside of the USA an possessions, please add $19.00 for surface postage and handling. For airmail add $65.00 in USA, Canada, and Mexico, $46.00 for surface airlift to Europe $65.00 for surface airlift to Japan, and $130.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevie Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical science, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views and recommendations as to medical procedures, choice of drugs and drug dosages are the responsibility of the authors.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

ELIMINATE THE TRAGEDY OF UNDETECTED ESOPHAGEAL INTUBATION FOREVER

A rapid color change indicates the Endotracheal tube is in the trachea.

FEF™ END-TIDAL CO_2 Detector
Small, simple, disposable

NOW WITH BREATH TO BREATH RESPONSE

For more information,
call our toll free number:
1-800-541-5799

U.S. Patent No: 4,728,499. Other U.S. & foreign patents pending.
©FENEM, Inc., 1988

FENEM™
AIRWAY MANAGEMENT SYSTEMS
Fenem, Inc., 84 William St. N.Y., N.Y. 10038
(212) 248-0220

Anesthesia and Analgesia

Contents

Volume 69 Number 1, July 1989

EDITORIAL

New Directions in Anesthesia Subspecialty Training? *J. G. Reves and Michael Nugent* 1

SCIENTIFIC ARTICLES

Negative Chronotropic Actions of Sufentanil and Vecuronium in Chronically Instrumented Dogs Pretreated with Propranolol and/or Diltiazem *William T. Schmeling, John P. Kampine, and David C. Warltier* 4

Spinal Cord Transmission of Impulses during High Spinal Anesthesia as Measured by Cortical Evoked Potentials *Eberhard Lang, Joerg U. Krainick, and Hans U. Gerbershagen* 15

Oral Transmucosal Fentanyl Citrate (Lollipop) Premedication in Human Volunteers *Theodore H. Stanley, Brian Hague, David L. Mock, James B. Streisand, Sally Bubbers, Ray R. Dzelzkalns, Peter L. Bailey, Nathan L. Pace, Katherine A. East, and Michael A. Ashburn* 21

Oral Transmucosal Fentanyl Citrate Premedication in Children *James B. Streisand, Theodore H. Stanley, Brian Hague, Hans van Vreeswijk, Gwan H. Ho, and Nathan L. Pace* 28

Hemodynamic and Cardiodynamic Effects of Propofol and Etomidate: Negative Inotropic Properties of Propofol *Thomas Brüssel, Josef L. Theissen, Gisli Vigfusson, P. Paul Lunkenheimer, Hugo Van Aken, and Peter Lawin* 35

Penile Block via the Subpubic Space in 100 Children *Bernard Dalens, Guy Vanneuville, and Pierre Dechelotte* 41

Incidence of Visceral Pain during Cesarean Section: The Effect of Varying Doses of Spinal Bupivacaine *Hilda Pedersen, Alan C. Santos, Ellen S. Steinberg, Howard M. Schapiro, Terry W. Harmon, and Mieczyslaw Finster* 46

Prolonged Nasotracheal Intubation and Its Association with Inflammation of Paranasal Sinuses *Argyro Fassoulaki and Philippos Pamouktsoglou* 50

Interaction of Lidocaine and Hypothermia in Bier Blocks in Volunteers *James E. Heavner, Lea Leinonen, Juhani Haasio, Juha Kytta, and Per H. Rosenberg* 53

Effects of Enflurane on Contractile Response of Canine Trachealis Muscle *Tetsuo Kochi, Masato Hagiya, and Tadanobu Mizuguchi* 60

Comparison of Viscoelastic Measures of Coagulation after Cardiopulmonary Bypass *Kenneth J. Tuman, Bruce D. Spiess, Robert J. McCarthy, and Anthony D. Ivankovich* 69

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

IARS 64TH CONGRESS

Friday, March 9 through Tuesday, March 13, 1990
Sheraton–Waikiki Hotel, Honolulu, Hawaii

CALL FOR PAPERS

AUGUST 4, 1989, DEADLINE

The Program Committee for the IARS 64th Congress cordially invites submission of abstracts for consideration as oral or poster presentations at the 1990 meeting in Hawaii. The official abstract application and transmittal forms are available from the Cleveland office of the IARS:

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, OH 44122, USA
Telephone: (216) 295-1124

Please note the absolute deadline for receipt of completed applications is August 4, 1989. Please request forms promptly—either by calling the telephone number above or returning the form below.

Noel W. Lawson, MD, Chairman
64th Congress Program Committee

- -

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122

Please send ______ abstract submission packet(s) for the IARS 64th Congress to:

Name: ____

Mail Address: ______________________________________

____

SCIENTIFIC ARTICLES—*continued*

Differing Effect of Agonist and Antagonist Muscle Relaxants on Cat Jaw Muscles — *A. F. L. Van Der Spek, P. I. Reynolds, J. A. Ashton-Miller, C. S. Stohler, and M. A. Schork* 76

Poststernotomy Neuralgia: A New Pain Syndrome — *Ray J. Defalque and Joel J. Bromley* 81

Humidity of the Bain and Circle Systems Reassessed — *Jan P. Bengtson, Anders Bengtson, Hans Sonander, and Ola Stenqvist* 83

Acute Acid Aspiration Lung Injury in the Rat: Biphasic Pathogenesis — *Thomas P. Kennedy, Kent J. Johnson, Robin G. Kunkel, Peter A. Ward, Paul R. Knight, and Jay S. Finch* 87

Comparison of Tracheal Intubating Conditions and Neuromuscular Blocking Profiles after Intubating Doses of Mivacurium Chloride or Succinylcholine in Surgical Outpatients — *M. E. Goldberg, G. E. Larijani, S. S. Azad, M. Sosis, J. L. Seltzer, J. Ascher, and J. N. Weakly* 93

REVIEW ARTICLE

Calcium, Calmodulin, and Anesthesiology — *Dennis F. Landers, Gerald L. Becker, and K. C. Wong* 100

CLINICAL REPORTS

Back Pain Following Epidurally Administered Nesacaine-MPF — *Eugene E. Fibuch and Susan E. Opper* 113

Airway Obstruction Caused by a Kinked Hi-Lo Jet^{R} Endotracheal Tube during High Frequency Jet Ventilation — *David H. Wilks, William C. Tullock, and Miroslav Klain* 116

Malignant Hyperthermia in a Hemodialysis Patient — *Tokuya Harioka, Tetsuhiro Sone, Hiroshi Toda, and Chiyomi Miyake* 119

Intrathecal Narcotics for Labor Revisited: The Combination of Fentanyl and Morphine Intrathecally Provides Rapid Onset of Profound, Prolonged Analgesia — *Barbara L. Leighton, Cheryl A. DeSimone, Mark C. Norris, and Bruce Ben-David* 122

Two Cardiac Arrests after Needle Punctures in a Patient with Mitral Valve Prolapse: Psychogenic? — *Zef A. Abraham and David Eric Lees* 126

Modification of an Eschmann Introducer to Permit Measurement of End-Tidal Carbon Dioxide — *Alan A. Artru, Allison B. Schultz, and Juan J. Bonneu* 129

Fatal Air Embolism in an Adolescent with Duchenne Muscular Dystrophy during Harrington Instrumentation — *Scott A. Lang, Peter G. Duncan, and Pierre R. Dupuis* 132

LETTERS TO THE EDITOR

An Inexpensive, Disposable Adapter for Increasing the Safety of Blind Nasotracheal Intubations — *Michael J. Dorsey and Brian R. Jones* 135

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1989 AWARDS

At the IARS 63rd Congress in March 1989, the Board of Trustees announced recipients of the 1989 Award as follows:

Evan D. Kharasch, MD, PhD, University of Washington School of Medicine, Seattle, WA:
"Human Endogenous Morphine and Codeine: Isolation, Mechanism of Synthesis, and Response to the Stress of Labor"

Bruce J. Leone, MD, Duke University School of Medicine, Durham, NC:
"Effects of Anesthesia on the Threshold of Pacing-Induced Myocardial Ischemia"

Donald H. Penning, BSc, MD, Lawson Research Institute, St. Joseph's Health Centre, University of Western Ontario, London, Ontario, Canada:
"The Role of Glutamic Acid in Perinatal Hypoxic/Ischemic Encephalopathy"

Marc Sabbe, MD, University of California San Diego, La Jolla, CA:
"Studies on the Effects of Spinally Administered Drugs on Respiratory Function"

Beverly J.M. Waxler, MD, Cook County Hospital, Chicago, IL:
"The Role of Proteinase Inhibitors in Anesthesiology"

1990 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1990 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **January 15, 1990.** Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1990 Award(s) will be announced at the Annual Scientific Meeting (64th Congress) of the International Anesthesia Research Society to be held at the Sheraton-Waikiki Hotel, Honolulu, Hawaii, March 9-13, 1990.

LETTERS TO THE EDITOR—*continued*

Multiple Nerve Palsies after Anesthesia—A Complication of Nitrous Oxide Use?	*Benjamin A. Lampert*	136
In Response	*Ashok A. Navalgund, Jonathan Jahr, Roland Gieraerts, Juei-Ling Chang, Glenn S. Price, and P. G. N. Garla*	137
Imprecise Fentanyl and Sufentanil Labels	*Robert W. Kennedy, William Till, and Jagdip B. Shah*	137
Perioperative Cardiovascular Collapse in a Patient Previously Treated with Doxorubicin	*Paul R. Hickey*	138
In Response	*A. Borgeat*	138
Heart Synchronized Ventilation during Extracorporeal Shock Wave Lithotripsy	*Eran Segal and Azriel Perel*	139
Nitroglycerine, Succinylcholine and Intraocular Pressure	*J. P. Jantzen, H. J. Hennes, and T. Wallenfang*	139
In Response	*V. K. Grover and Suman Sharma*	141
Smithisms	*Ray T. Smith, Jr.*	141
Limit(ation)s for ACT	*David R. Jobes, Norig Ellison, and Frederick W. Campbell*	142
In Response	*Glenn P. Gravlee*	143

BOOK REVIEWS

General Anaesthesia 5th Edition	*Norig Ellison*	145
Clinical Anesthesia	*Isaac Azar*	145
Effective Hemostasis in Cardiac Surgery	*Richard F. Davis*	146
Illustrated Manual of Regional Anesthesia	*Aaron J. Gissen*	147

Historical Notes	14 118

NOW PUBLISHED BY ELSEVIER

Editor

Raymond A. Dionne, DDS, PhD, National Institute of Dental Research,
Bethesda, MD

Anesthesia Progress

A Journal for Pain and Anxiety Control

Editorial Review Panel
Glenn Clark, DDS, MS, University of California, Los Angeles
Stephen Cooper, DMD, PhD, University of Pennsylvania
Paul Desjardins, DMD, PhD, University of Medicine and Dentistry of New Jersey
Tommy Gage, DDS, PhD, Baylor University, Texas
John Gregg, DDS, PhD, Blacksburg, Virginia
Milton Houpt, DDS, PhD, University of Medicine and Dentistry of New Jersey
Barbara Melamed, PhD, University of Florida
Paul Moore, DMD, PhD, University of Pittsburgh, Pennsylvania
Michael Roizen, MD, University of Chicago
Allen Sisk, DDS, Medical College of Georgia
John Yagiela, DDS, PhD, University of California, Los Angeles
Editorial Consultant
Henry M. Koehler

Anesthesia Progress, the premier journal devoted to the management of patient pain and anxiety in dentistry, is now published by Elsevier. Established over 30 years ago, **Anesthesia Progress** is a highly respected, peer-reviewed journal reporting current information for professionals in the field of anesthesia and pain control.

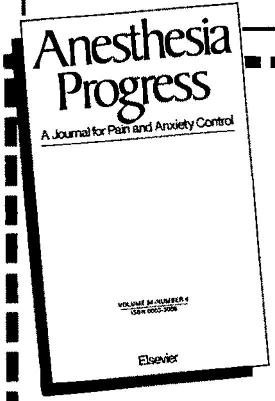
Anesthesia Progress, the official journal of the American Dental Society of Anesthesiology, features clinical and research articles, review articles, case reports, literature reviews, meeting updates, letters to the editor, and a Continuing Education Calendar. The journal's rigorous peer review process ensures the reader a wealth of scientifically valid, practical information on the safe and effective treatment of patient pain and anxiety.

In order to provide the widest possible coverage of the field, **Anesthesia Progress** reports on all of the following topics:

- **general anesthesia**
- **conscious sedation**
- **local anesthesia**
- **analgesics**
- **IV sedation**
- **chronic pain**
- **pediatric sedation**
- **behavioral methods of anxiety control**
- **drug-induced emergencies**
- **education in pain and anxiety control**
- **evaluation of new and standard drugs**

Anesthesia Progress is abstracted/indexed in ***Biological Abstracts*** (BIOSIS), ***Excerpta Medica*** (EMBASE), ***Index to Dental Literature*** (MEDLINE), ***Periodicals Digest in Dentistry.***

1989 Subscription Information
Volume 36 (6 issues), 1989. ISSN 0003-3006
Institutional rate: $60.00. Personal rate: $38.00


Anesthesia Progress
A Journal for Pain and Anxiety Control
Elsevier

ORDER FORM

Anesthesia Progress ISSN 0003-3006
Volume 36 (6 issues) 1989
Please enter my 1989 subscription at the following rate:
☐ Institutional: $60.00 ☐ Personal: $38.00
(Note: Please add $21.00 for postage and handling outside the U.S.)
☐ Please send me a free sample copy.

Payment
Enclosed is my:
☐ personal check ☐ bank draft
Please charge to:
☐ American Express ☐ VISA
☐ MasterCard (issuing bank #__________)
Account #__________ Expires ______
Signature ________________

☐ **Please bill me.** (Personal subscriptions must be prepaid by check or charge card. Orders from non-U.S. customers must be prepaid.)
Name________________
Address________________
City________________
State________ Zip/Postal Code________

For sample copies send to:
in North America:
Elsevier Science Publishing Co., Inc.
P.O. Box 882, Madison Square Station
New York, NY 10159
in the rest of the world:
Elsevier Science Publishers, Direct Mail Department, P.O. Box 211, 1000 AE Amsterdam, The Netherlands

Note: Send subscription orders to the New York address. Subscription rates valid until December 31, 1989. Please allow 6-8 weeks for delivery of the first issue.

10/88 V9AF BILL828A

ANESTH ANALG
1989;69:1–3

Editorial

New Directions in Anesthesia Subspecialty Training?

J. G. Reves, MD, and Michael Nugent, MD

Key Words: EDUCATION—specialty training.

The academic year 1988–1989 inaugurated an obligatory (CA–3) year of training in clinical anesthesia for American Board of Anesthesiology (ABA) certification. Thus, to be American Board of Anesthesiology eligible, a resident must complete a continuum of education in anesthesiology consisting of four years of training subsequent to the award of medical or osteopathic degree. The curriculum includes 12 additional months of non–anesthesia clinical training (clinical base) and 36 months of gradual and increasingly complex clinical training in anesthesia (CA–1, CA–2, and CA–3 years). The new CA–3 year in the ABA educational continuum is termed the "advanced anesthesia training" experience. It may be constructed in one of three ways: 1) advanced clinical track, 2) subspecialty track, or 3) clinical scientist track. The ABA has identified obstetric anesthesia, pediatric anesthesia, cardiothoracic anesthesia, neuroanesthesia, anesthesia for outpatient surgery, recovery room care, intensive care, regional anesthesia, and pain management as clinical subspecialty areas appropriate for the CA–3 year (1). A trainee in the new curriculum can spend blocks of time from 2 months of 12 months in one of the eight subspecialty disciplines. The subspecialty clinical track consists of 9 to 12 months in one subspecialty or 6 and 6 months in each of two subspecialty areas.

Any educational change can have one of two results: better or worse. Although some have argued that the length of this new curriculum will not appreciably change anesthesia training, this conclusion is in our opinion unlikely. Whether lengthening of th curriculum will have a positive effect on overa anesthesia training remains to be proven: We suspe that an additional year of training might produ better "general" anesthesiologists. However, the p tential for a negative effect on subspecialty training real, so real it deserves discussion with, perhap either solution or avoidance of the problems we se facing subspecialty training in anesthesia. We suspe that these problems exist outside the USA; indee they face anesthesia educators throughout the worl

The goal of subspecialty training is to teach th residents a clinical practice complete with requisi skills as well as a body of knowledge that can b found in the literature: general anesthesia textbook subspecialty anesthesia textbooks, general anesthes literature, subspecialty anesthesia journals, and me ical specialty journals. Although there is no certific tion process for anesthesia subspecialties except f those involving critical care, there most certainly is body of knowledge in each subspecialty that can on be mastered by some variable (most assuredly) b finite (just as assuredly) time of study. Likewise the must be some requisite, as yet undefined but neve theless real, period of time required to achieve tr expertise in each clinical subspecialty. To gain th knowledge and to master clinical skills required i subspecialty practice certainly requires at least o year, but without examination and certification pr cess whether this year is indeed long enough for a subspecialties cannot be proven.

Why is a year of subspecialty training the min mum required? The answer is that even the mo gifted anesthesia resident needs this time to read th anesthesia and related literature (e.g., in cardi anesthesia there are at least six journals) with whic this subspecialist must be familiar, and a host of text Also, within the course of a few months (three to si say), the resident will not encounter first or secon

---

Received from the Department of Anesthesiology, the Heart Center, Duke University, Box 3094, Durham, North Carolina, and the Mayo Clinic, Rochester, Minnesota. Accepted for publication February 8, 1989.

Address correspondence to Dr. Reves, Department of Anesthesiology, Duke University, Box 3094, Durham, NC 27710.

©1989 by the International Anesthesia Research Society

hand (via his fellow subspecialty physicians) the number of cases required to provide the experience necessary to have the confidence and competence that comes only from "having been there." We know no minimal number of cases, types of cases, or clinical encounters with complications that are required to achieve the necessary experience, but in years past it has been generally agreed that 6 to 12 months were necessary to obtain this clinical expertise. Previously, this 6 to 12 months of experience was obtained during an elective CA–3 year. As the number of cases available during the CA–3 year remains virtually unchanged, but the number of CA–3 residents exposed to them will significantly increase with the new curriculum mandating a CA–3 year for all residents, the quality of subspecialty clinical experience will be inevitably diluted so that 6 months exposure, once considered adequate, will now become inadequate.

Another problem centers around the fact that research is an important if not essential element in the training of subspecialty residents. If residents are not trained to do research during their anesthesia residency, how will they learn this activity so absolutely necessary to the advancement of our specialty? Subspecialty research is the most likely vehicle by which clinical research can be conducted since clinical research requires the cooperation of surgeons and others in the operating room. Subspecialists by their clinical commitment have earned the cooperation of coworkers who not only facilitate the research but intellectually contribute to it. The subspecialty surgeon and anesthesiologist know the important questions and together can answer them in a joint effort that is less easily achieved without the subspecialty collaborative link. Because research is vital to the subspecialty trainee, he or she must be given adequate time to participate in it. We believe a minimum of one year is required for the trainee to have adequate exposure to clinical research in order to be able to successfully conduct independent clinical research programs following completion of training. Basic science or bench research is also a desirable element in the subspecialty training, but this requires at least yet another year of total commitment to the learning of basic science investigation. In cardiovascular anesthesia subspecialty training, for example, by working in the laboratory of an established investigator in an area such as myocardial metabolism, the trainee will gain essential investigative experience. The trainee would be expected to master the requisite knowledge, skills, and method of laboratory research, including the "art" of grant procurement. Thus, the duration of subspecialty training depends on the objectives and while one year might be adequate in some instances, as much as three years might be required, a fact not taken into account in the new ABA–mandated CA–3 year requirement.

We predict that another problem facing subspecialty training will be a decrease, not increase, of the absolute number of CA–3 trainees who "elect" to spend 6 to 12 months in subspecialty training. This decision may not be by the residents' own volition but simply a result of the program directors' need to incorporate the greater number of residents at the CA–3 level into the various subspecialty training areas. The CA–3 year is an advanced anesthesia training experience that requires resident assignment to have more difficult or complex anesthesia procedures, many of which are in the subspecialty areas. The ability to accommodate CA–3 residents for a full year's tenure in a single subspecialty is hampered by the fact that there is the need to rotate all or most CA–3 residents through subspecialty services to fulfill the ABA requirement of increasingly difficult cases. Thus popular subspecialty rotations where one or two CA–3 residents had spent an elective year previously (prior to the new curriculum) may indeed be staffed by four to eight residents spending only 2 to 3 month rotations on the particular subspecialty service. Whether this will indeed happen needs to be determined. As we do not know the optimal number of subspecialty anesthesiologists, the reduction in the number trained each year does not necessarily signify a negative effect of the curriculum, but we believe this is a major concern. The net result may be that with the new curriculum we may not produce enough well–trained anesthesia subspecialists.

The addition of a dedicated subspecialty fellowship program to be completed after the CA–3 year might reestablish the training of a group of subspecialists dedicated to the clinical practice and research specific to their subspecialty areas. After completion of a post CA–3 subspecialty fellowship, these trainees would move into either private practice or academics with levels of expertise and enthusiasm that would allow for continued growth and development of anesthesiology into new areas. It would not be necessarily expected that all who practice in a subspecialty area have subspecialty certification or that subspecialists would only practice in their areas of expertise. Within any anesthesia group in an academic or community hospital, graduates of the fellowship year would be leaders keeping up with a rapidly expanding body of knowledge and providing leadership in their area of subspecialization.

We propose the following steps to address our concerns about the direction the new curriculum takes in subspecialty education. First, data regarding the effect of the new curriculum on the number and duration of study of residents in subspecialty education must be gathered. It is relatively easy to record the change (if any) that is wrought by the curriculum on the number of trained subspecialists. Second, the education committees of the various anesthesia subspecialty organizations should develop curricula and propose guidelines for tenures of clinical exposure. Third, the feasibility and necessity for creating a CA–4 fellowship for the training of subspecialists must be explored by program directors, the ABA, and educators in anesthesiology. Funding for the additional year needs to be justified and secured. Fourth, the question of whether anesthesia subspecialty certification is necessary must be answered. We have ABA sanctioned certification in critical care; should we have it for the other anesthesia subspecialties? The answer to this question would reveal whether, in fact, the new curriculum has favorably affected education in anesthesia subspecialties. We think it is time to develop subspecialty anesthesia curricula, establish training guidelines, and plan subspecialty certification.

In summary, a prosperous anesthesia subspecialty training is vital for the development of clinical and academic excellence in anesthesiology. There have been great advances in subspecialty training in the recent past and this must continue as the anesthesia training programs evolve. As subspecialty anesthesia practices have matured, quality of clinical care and the professional esteem in which we are held by our colleagues in other medical specialties has improved. We share the view stated by the cardiac surgeon Dr. John Kirklin, "For the anesthesiologist to reach his or her potential and for the patient to receive the best care, the anesthesiologist should be a specialist in cardiovascular anesthesia and supportive treatment" (2). This opinion applies not just to cardiac anesthesia but to all subspecialties of anesthesiology. Certainly we do not need to train only subspecialists, but we must educate a significant number if the field of anesthesiology is to progress at an optimal rate. We need to ask if the new ABA educational continuum will educate better subspecialists, more or less subspecialists, and if the new ABA curriculum will lead us in the direction of better subspecialty training: we are fearful that the answer is no.

References

1. American Board of Anesthesiology. A modification in the training requirements in anesthesiology: Requirements for the third clinical anesthesia year. Anesthesiology 1985;62:175–7.
2. Kirklin JW, Barrett Boyce BG. Cardiac surgery. New York: John Wiley & Sons, 1986:61.

Negative Chronotropic Actions of Sufentanil and Vecuronium in Chronically Instrumented Dogs Pretreated with Propranolol and/or Diltiazem

William T. Schmeling, MD, PhD, John P. Kampine, MD, PhD, and
David C. Warltier, MD, PhD

SCHMELING WT, KAMPINE JP, WARLTIER DC. Negative chronotropic actions of sufentanil and vercuronium in chronically instrumented dogs pretreated with propranolol and/or diltiazem. Anesth Analg 1989;69:4–14.

Patients with ischemic heart disease who present for surgery are frequently managed with a "high dose" narcotic technique utilizing fentanyl or sufentanil in combination with neuromuscular blockade. Narcotic anesthetic induction has been associated with perioperative cardiac conduction disturbances, particularly in patients previously treated with calcium channel and/or beta-adrenergic antagonists. The purpose of the present investigation was to examine in chronically instrumented dogs the effects on systemic and coronary hemodynamics and regional contractile function of sufentanil alone or in combination with the nondepolarizing neuromuscular blocking agent vecuronium, with and without pretreatment with the calcium channel blocking agent diltiazem, and/or the beta-adrenergic antagonist propranolol.

Thirty-six experiments were conducted in four groups of 19 chronically instrumented dogs. Administration of sufentanil (25 and 50 μg/kg of normal body weight IV) resulted in a significant sinus or junctional bradyarrhythmia without alteration in systemic and coronary hemodynamics. Pretreatment with propranolol (1 mg/kg IV) decreased left ventricular +dP/dt without other hemodynamic alterations. After propranolol pretreatment, sufentanil (25 and 50 μg/kg IV) produced statistically significant dose-dependent decreases in heart rate and +dP/dt, while increasing mean and diastolic coronary vascular resistances. After pretreatment with diltiazem (0.3 mg/kg IV) and propranolol (1.0 mg/kg IV), sufentanil (25 μg/kg IV) produced significantly greater bradycardia (38 ± 4 beats/min) than it did in non-pretreated or propranolol-pretreatment dogs. Similarly, administration of sufentanil (25 μg/kg IV) in combination with vecuronium (0.1 mg/kg IV) after propranolol and diltiazem pretreatment resulted in the appearance of bradyarrhythmias (32 ± 2 beats/min) and two episodes of asystole, responsive to atropine sulfate (0.4 mg). In spite of severe bradycardia, arterial pressure was well maintained in all groups. In all groups, administration of naloxone (0.2 mg/kg IV and 0.2 mg/kg IM) after sufentanil produced significant increases in arterial pressure, left ventricular +dP/dt, and diastolic coronary blood flow velocity.

Therefore, the combination of sufentanil and vecuronium in chronically instrumented dogs may result in the appearance of cardiac conduction disturbances. This action is more likely to occur after pretreatment with diltiazem and propranolol. Although systemic hemodynamics were well maintained in dogs in the present study during the episodes of bradyarrhythmias, potentially significant cardiovascular deficits may occur in patients with coronary artery disease or those with valvular heart disease dependent on a greater heart rate for maintenance of cardiac output.

Key Words: ANALGESICS, SUFENTANIL. ANESTHETICS, INTRAVENOUS—sufentanil. HEART—DILTIAZEM. PHARMACOLOGY—diltiazem. NEUROMUSCULAR RELAXANTS—vecuronium.

Previous studies have demonstrated the efficacy of combined calcium channel and beta-adrenergic blockade in the treatment of ischemic heart disease (1–3). Patients with such ischemic heart disease who present for surgery are frequently managed with a "high dose" narcotic technique in combination with neuromuscular blockade. Such techniques frequently employ the narcotic agonists fentanyl and sufentanil

---

Received from the Departments of Anesthesiology, Pharmacology, and Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin and the Veterans Administration Medical Center, Wood, Wisconsin. Accepted for publication January 12, 1989.

Supported in part by USPHS Grant HL 36144 and Veterans Administration Medical Research Funds, Veterans Administration, Wood, Wisconsin.

Address Correspondence to Dr. Schmeling, Departments of Anesthesiology and Pharmacology and Toxicology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226.

©1989 by the International Anesthesia Research Society

and are associated with hemodynamic stability and low heart rates (4), thereby minimizing perturbations in myocardial oxygen supply and demand (5). However, narcotic anesthetic induction has been associated with malignant perioperative conduction disturbances including bradyarrhythmias resulting in hypotension after the administration of sufentanil and vecuronium (6,7) or fentanyl and pancuronium (8). In these reports, all patients received either beta-adrenergic antagonists alone or in combination with slow channel calcium blocking agents. The potential for adverse interactions of such combined beta-and calcium channel blockade has been previously described (9).

Most studies of the cardiovascular pharmacology of narcotic agonists, neuromuscular blockers, beta-adrenergic blockers, and calcium channel blockers have been conducted in acute, open chest preparations with an unrelated baseline anesthetic. Profoundly different hemodynamic states exist between conscious and anesthetized animals (10). The purpose of the present investigation was to examine the hemodynamic and electrocardiographic (ECG) effects of sufentanil alone or in combination with the nondepolarizing neuromuscular relaxant vecuronium, with and without pretreatment with the calcium channel blocking agent diltiazem, and/or the beta-adrenergic antagonist propranolol in chronically instrumented dogs. In addition, the actions of narcotic reversal by naloxone on hemodynamics and ECG responses were also evaluated.

Materials and Methods

General Preparation

Anesthesia was induced in 19 conditioned, fasting mongrel dogs weighing between 22 and 30 kg with sodium thiamylal (10 mg/kg of normal body weight IV). After tracheal intubation, anesthesia was maintained with halothane (1.0% to 1.5%) in oxygen with use of a semiclosed circuit with a Monaghan 300 d/m ventilator. Arterial blood gas tensions were maintained within normal limits during surgery and in all experiments by adjustment of ventilation and administration of 1.5% sodium bicarbonate, as required. Under sterile conditions, a thoracotomy was performed in the left fifth intercostal space and the lungs gently retracted. The heart was supported by a pericardial cradle and heparinized catheters were inserted into the thoracic aorta and right atrium for measurement of aortic blood pressure and for intravenous drug administration.

A 1.5- to 2.0-cm section of the proximal left anterior descending coronary artery (distal to the first diagonal branch) was carefully isolated by blunt dissection. A Doppler ultrasonic flow transducer (20 MHz) (Hartley Instruments) was positioned around the vessel for measurement of phasic and mean coronary blood flow velocity. Relative mean coronary vascular resistance (ru) was determined by dividing mean arterial pressure (mm Hg) by mean coronary blood flow velocity (Hz $\times$ 10^2).

A Konigberg high fidelity miniature micromanometer (P7) was positioned in the left ventricular chamber through a stab wound in the apex for recording of left ventricular pressure. Direct measurements of left ventricular pressure were cross-correlated with measurements obtained from the left atrial and aortic catheters. The maximal rate of rise of left ventricular pressure (peak positive dP/dt), an index of global left ventricular contractility, was obtained by electronic differentiation of the ventricular pressure wave form. A triangular wave signal with known slope was used to calibrate the differentiator. All catheters and leads were secured, tunneled subcutaneously and exteriorized between the scapulae by a small incision. The chest wall was closed in layers and the pneumothorax evacuated by a chest tube with suction drainage. Before each experiment, small pregelled cutaneous electrodes were taped to the appropriate limbs for measurement of the ECG (limb lead II).

Postoperatively, each dog recovered for 7 to 10 days before experimentation. Animals were treated with oral chloramphenicol (1.5 gm twice daily) and trained to stand quietly in a sling during this period. All experiments were conducted with the dog supported in the sling.

Evaluation of segmental contractile function. Regional myocardial contractility (percent segment shortening) was measured in the perfusion territory of the left anterior descending coronary artery by pairs of miniature tubular ultrasonic crystals. Crystals were inserted parallel to muscle fiber orientation perpendicular to the long axis of the left ventricle, within the subendocardium of the left ventricular free wall (10 to 15 mm apart and 10 mm deep). The leads of each crystal were connected to an ultrasonic amplifier (Hartley, Houston, TX), which transformed the sound pulse transmitted into an electronic signal proportional to the distance between the two cylindrical crystals. The crystals were precalibrated, and the tracings monitored continuously with use of a Tektronix 2215A oscilloscope. By recording changes in transmission time, the distance between the two crystals was measured. End-systolic segment length (ESL) and end-diastolic segment length (EDL) were derived from the analog signals at points corresponding to maximal −dP/dt and the onset of left ventricular isovolumetric contraction, respectively. Percent segment shortening (%SS) was calculated with use of the equation

$$\%SS = \frac{(EDL - ESL) \times 100.}{EDL}$$

The lengths were normalized according to the method of Theroux et al. (11). Each measure of segment function represented the average of eight consecutive cardiac cycles. All hemodynamic data were recorded continuously on a Hewlett-Packard polygraph and digitized with a microcomputer interfaced with an analog to digital converter and analyzed as previously described (12).

Experimental Protocol

After implantation and verification that placement in the sling produced no stress or anxiety-induced alterations in hemodynamics, dogs fasted for 8 hr before experimentation. Fluid replacement was with normal saline solution. Animals were randomly assigned to four experimental protocols. No dog was utilized more than once in any experimental protocol. Three- to five-day periods were allowed between experiments on any one animal.

Experiment A: Hemodynamic alterations produced by sufentanil. Initial control experiments were completed to determine the hemodynamic actions of sufentanil (25 and 50 μg/kg). After establishing and quantifying baseline hemodynamics and regional myocardial function in the awake, unsedated state, dogs were given an intravenous infusion of sufentanil citrate at a dose of 25 μg/kg over 5 to 10 min and were then intubated and artificially ventilated.

Hemodynamic parameters were constantly monitored and 15 min after the 25 μg/kg dose was completed and a stable hemodynamic state obtained, a second dose of sufentanil (50 μg/kg) was infused over 10–15 min. Hemodynamics were again recorded during a stable hemodynamic state. Thirty minutes after completing the second infusion of sufentanil, narcotic reversal was accomplished with naloxone (0.2 mg/kg IV and 0.2 mg/kg IM) and hemodynamic alterations recorded 15 min later.

Experiment B: Hemodynamic alterations produced by sufentanil after propranolol pretreatment. Experiments were accomplished in a similar fashion to Experiment A, except that after establishing and recording baseline conscious hemodynamics, the beta-blocker propranolol (1.0 mg/kg IV) was administered. Fifteen minutes after administration of propranolol, dogs were given 25 μg/kg followed by 50 μg/kg sufentanil and subsequent naloxone reversal in a fashion similar to that described for Experiment A.

Experiment C: Hemodynamic alterations produced by sufentanil after propranolol and diltiazem pretreatment. Experiments were accomplished in a similar fashion to Experiment B, however, after administration of propranolol, the calcium channel blocker diltiazem was infused intravenously (300 μg/kg at a rate of 15 μg/kg/min). Ten to fifteen minutes after completion of diltiazem infusion, administration of sufentanil (25 μg/kg) followed by naloxone reversal was accomplished as in Experiment A.

Experiment D: Hemodynamic alterations produced by sufentanil and vecuronium after propranolol and diltiazem pretreatment. These experiments were accomplished in a similar fashion to Experiment C, except that after administration of propranolol and diltiazem, sufentanil (25 μg/kg) combined with the neuromuscular relaxant vecuronium (0.1 mg/kg) was infused. Fifteen to thirty minutes later, reversal doses of naloxone (0.2 mg/kg IV and 0.2 mg/kg IM), neostigmine (0.05 mg/kg) and glycopyrolate (7.0 μg/kg) were administered and hemodynamic alterations quantitated.

Statistical Analysis

Data are presented as means ± SEM. Changes in hemodynamics were analyzed with use of SAS software with an unbalanced ANOVA in GLM followed by Bonferroni's modification of the *t* test. Changes in each experiment were compared against the awake, unsedated state for that experiment at each pharmacological intervention and considered significant when the probability (*P*) value was less than 0.05. Additionally, the effect of interexperimental pretreatments was analyzed for the major hemodynamic indexes of heart rate and systolic, diastolic, and mean arterial pressures, with use of GLM followed by Bonferroni's modification of the *t* test as well as by a repeated measures ANOVA of contrast variables to determine trending.

Results

Experiment A: Hemodynamic alterations produced by sufentanil. The hemodynamic effects of sufentanil (25

Table 1. Hemodynamic Actions of Sufentanil in Chronically Instrumented Dogs

	N	Conscious	Sufentanil (25 μg/kg)	Sufentanil (50 μg/kg)	Naloxon (0.2 mg/k
Heart rate-systolic pressure product (beats/min × mm Hg × 10^3)	7	9.6 ± 1.2	7.6 ± 0.4	5.3 ± 0.8*	15.9 ± 0.
Left ventricular systolic pressure (mm Hg)	8	122 ± 3	147 ± 4	130 ± 5	153 ± 8*
Left ventricular end diastolic pressure (mm Hg)	8	9 ± 1	16 ± 1	15 ± 2	12 ± 3
+dP/dt (mm Hg/sec)	8	2612 ± 152	3016 ± 135	2640 ± 210	3712 ± 42
Diastolic coronary blood flow velocity (Hz × 10^2)	8	48 ± 8	56 ± 8	48 ± 7	89 ± 15
Mean coronary blood flow velocity (Hz × 10^2)	8	27 ± 5	25 ± 5	21 ± 4	50 ± 9*
Diastolic coronary vascular resistance (ru)	7	2.63 ± 0.53	2.90 ± 0.94	2.99 ± 0.92	2.01 ± 0.
Mean coronary vascular resistance (ru)	7	4.65 ± 0.85	6.89 ± 2.02	6.83 ± 1.78	3.61 ± 0.
Segment shortening (%)	7	19.0 ± 2.5	20.1 ± 2.6	20.1 ± 2.6	19.2 ± 2.

Mean ± SEM data.
*Significantly different ($P < 0.05$) from the conscious state.

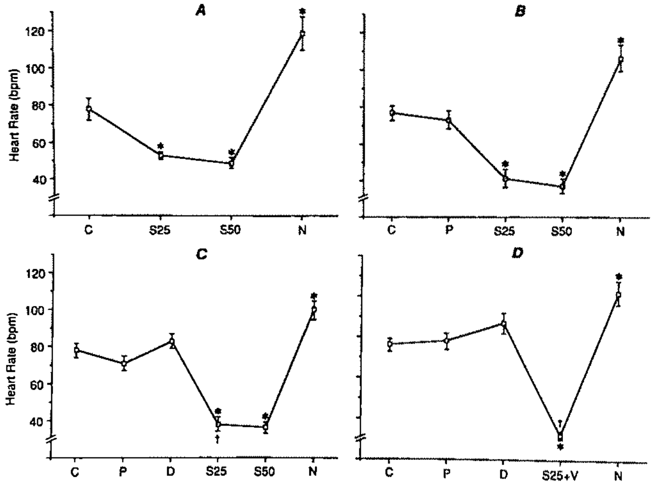


Figure 1. Effect of sufentanil alone (25 [S25] and 50 [S50] μg/kg) on heart rate alone (Experiment A, N = 9), and after pretreatment with propranolol (P) (Experiment B, N = 8), or propranolol plus diltiazem (D) (Experiment C, N = 8), or in combination with vecuronium (V) (Experiment D, N = 11). *significantly different from conscious control ($P < 0.05$); †significantly different from dogs without pretreatment ($P < 0.05$). N = naloxone; C = conscious control.

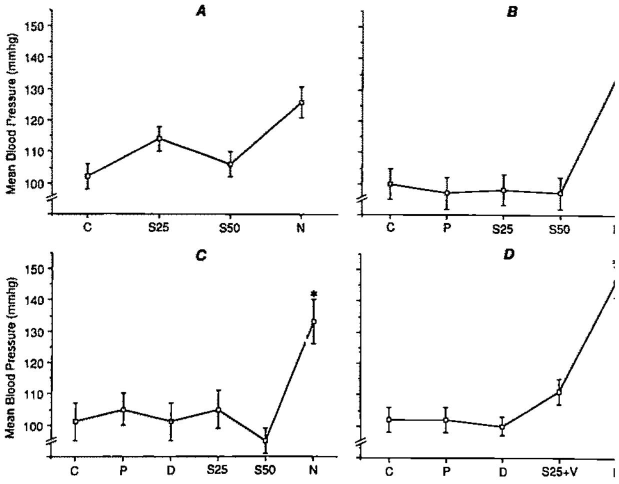


Figure 2. Effect of sufentanil alone (25 [S25] and 50 [S50] μg/kg) mean arterial pressure alone (Experiment A, N = 7), and af pretreatment with propranolol (P) (Experiment B, N = 7), propranolol plus diltiazem (D) (Experiment C, N = 7), or combination with vecuronium (V) (Experiment D, N = 1 *significantly different from conscious control ($P < 0.05$). N naloxone; C = conscious control.

and 50 μg/kg) are summarized in Table 1. In Tables 1–4 and Figures 1 and 2, unequal numbers of measurements represent catheter and/or instrument failure after implantation but before experimentation. Low and high doses of sufentanil significantly decreased heart rate (Figure 1) (78 ± 6 to 53 ± 2 and 49 ± 3 beats/min, respectively) without change in arterial pressure (Figure 2). The predominant cardiac rhythm observed after administration of sufentanil was sinus bradycardia (seven of nine dogs). In three of the nine animals, a sinus bradycardia combined with high degree atrioventricular block resulted in a junctional escape rhythm with an occasional conducted premature atrial contraction (Figure 3). Coronary blood flow velocity and indexes of left ventricular contractility, including peak positive dP/dt and segment shortening, were essentially unchanged from the conscio state.

Naloxone significantly increased heart rate abo heart rate levels in conscious dogs (78 ± 6 to 119 ± beats/min). Arterial pressure, rate-pressure produ and left ventricular systolic pressure were signi cantly elevated. Naloxone also increased left ventri ular +dP/dt and diastolic and mean coronary blo flow velocities.

Experiment B: Hemodynamic alterations produced sufentanil after propranolol pretreatment. Hemodynam effects of pretreatment with propranolol and subs quent administration of sufentanil are summarized Table 2. Propranolol significantly decreased left ve tricular +dP/dt (2464 ± 146 to 1941 ± 99 mm Hg/se

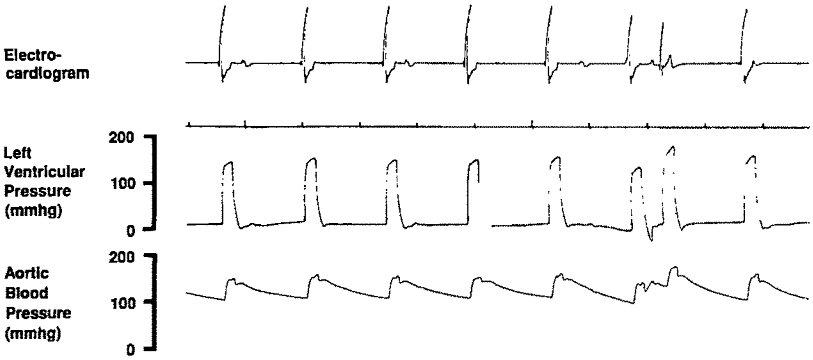

Electro-cardiogram
Left Ventricular Pressure (mmhg)
200
100
0
Aortic Blood Pressure (mmhg)
200
100
0

Figure 3. Electrocardiogram and left ventricular and aortic pressure traces after administration of 25 μg/kg sufentanil without pretreatment (Experiment A). Note the sinus bradycardia with high degree atrioventricular block and nodal escape rhythm.

Table 2. Hemodynamic Actions of Sufentanil After Pretreatment With Propranolol (1.0 mg/kg) in Chronically Instrumented Dogs

	N	Conscious	Propranolol (1 mg/kg)	Sufentanil (25 μg/kg)	Sufentanil (50 μg/kg)	Naloxone (0.2 mg/kg)
Heart rate-systolic pressure product (beats/min × mm Hg × 10^3)	7	9.5 ± 0.7	8.2 ± 0.7	5.0 ± 0.7*	4.3 ± 0.6*	15.9 ± 1.3*
Left ventricular systolic pressure (mm Hg)	9	114 ± 6	110 ± 5	114 ± 6	113 ± 7	143 ± 6*
Left ventricular end diastolic pressure (mm Hg)	9	9 ± 0.5	10 ± 1.0	14 ± 1.7	14 ± 1.3	19 ± 2.9*
+dP/dt (mm Hg/sec)	9	2464 ± 146	1941 ± 99*	1575 ± 101*	1579 ± 113*	2116 ± 146*
Diastolic coronary blood flow velocity (Hz × 10^2)	8	53 ± 5	54 ± 5	41 ± 4	44 ± 9	80 ± 13*
Mean coronary blood flow velocity (Hz × 10^2)	8	29 ± 3	30 ± 3	17 ± 2	18 ± 2	47 ± 9*
Diastolic coronary vascular resistance (ru)	7	2.09 ± 0.11	2.00 ± 0.11	2.76 ± 0.23	2.99 ± 0.32*	2.25 ± 0.32
Mean coronary vascular resistance (ru)	7	3.90 ± 0.25	3.63 ± 0.27	6.31 ± 1.01*	6.66 ± 0.99*	3.96 ± 0.62
Segment shortening (%)	7	17.9 ± 5.0	16.0 ± 3.6	14.7 ± 4.6	14.0 ± 3.4	12.4 ± 4.4

Mean ± SEM data.
*Significantly different ($P < 0.05$) from the conscious state.

No other hemodynamic change was observed. Normal sinus rhythm was present in all eight animals after the administration of propranolol. Subsequent administration of sufentanil (25 and 50 μg/kg) resulted in a decrease in heart rate to 41 ± 5 and 37 ± 4 beats/min, respectively (Figure 1). In two of the eight animals, the cardiac rhythm after administration of 25 μg/kg sufentanil consisted of sinus bradycardia with an occasional junctional rhythm. In six of the eight animals, a slow junctional rhythm predominated with occasional periods of sinus bradycardia. The addition of 50 μg/kg sufentanil caused further slowing of the junctional rhythm with decreased periods of conducted sinus beats.

After propranolol pretreatment, sufentanil produced significant decreases in +dP/dt as well as increasing mean coronary vascular resistance in a dose-related manner. Administration of naloxone (0.2 mg/kg) increased heart rate, arterial pressure, left ventricular systolic and end diastolic pressures, and +dP/dt and coronary blood flow velocity.

Experiment C: Hemodynamic alterations produced by sufentanil after propranolol and diltiazem pretreatment. Pretreatment with propranolol produced results similar to those observed in Experiment B (Table 3). Subsequent treatment with diltiazem (0.3 mg/kg) did not produce any further change in hemodynamics. Cardiac rhythm remained normal sinus in all animals. After diltiazem and propranolol pretreatment, administration of 25 and 50 μg/kg sufentanil produced results similar to those of Experiment B (Figures 1 and 2). The predominant cardiac rhythms present after administration of sufentanil (25 μg/kg) consisted of severe sinus bradycardia in six of eight animals and a junctional rhythm without sinus activity in two animals. Administration of 50 μg/kg of sufentanil resulted in further slowing of the junctional rhythm and occasional conducted sinus beat (Figure 4). The change in heart rate (78 ± 4 to 38 ± 4 beats/min) produced by the low dose of sufentanil after pretreatment with propranolol and diltiazem was significantly different than the same dose of sufentanil without pretreatment (Experiment A) or propranolol (without diltiazem) pretreatment (Experiment B). Both the low and high doses of sufentanil significantly increased left ventricular end diastolic pressure. Administration of naloxone produced hemodynamic changes similar to those observed in Experiments A or B.

Table 3. Hemodynamic Actions of Sufentanil After Pretreatment With Propranolol (1.0 mg/kg) and Diltiazem (0.3 mg/kg) in Chronically Instrumented Dogs

	N	Conscious	Propranolol (1 mg/kg)	Diltiazem (0.3 mg/kg)	Sufentanil (25 μg/kg)	Sufentanil (50 μg/kg)	Naloxone (0.2 mg/kg)
Heart rate-systolic pressure product (beats/min × mm Hg × 10^3)	7	9.2 ± 0.8	8.4 ± 0.7	9.6 ± 0.8	4.9 ± 0.7*	4.2 ± 0.4*	14.1 ± 1.0*
Left ventricular systolic pressure (mm Hg)	7	115 ± 5	116 ± 5	114 ± 4	118 ± 5	113 ± 4	142 ± 7*
Left ventricular end diastolic pressure (mm Hg)	7	9 ± 0.7	11 ± 1.6	10 ± 1.7	17 ± 1.7*	15 ± 1.8*	20 ± 2.4*
+dP/dt (mm Hg/sec)	7	2557 ± 265	2130 ± 175*	2116 ± 168*	1664 ± 158*	1579 ± 116*	2040 ± 91*
Diastolic coronary blood flow velocity (Hz × 10^2)	8	50 ± 8	53 ± 9	62 ± 9	48 ± 9	47 ± 11	92 ± 26*
Mean coronary blood flow velocity (Hz × 10^2)	8	27 ± 4	29 ± 5	33 ± 5	17 ± 3	17 ± 3	54 ± 16*
Diastolic coronary vascular resistance (ru)	7	2.67 ± 0.44	2.68 ± 0.41	2.14 ± 0.37	3.49 ± 0.94	3.00 ± 0.48	2.30 ± 0.28
Mean coronary vascular resistance (ru)	7	4.81 ± 0.73	4.84 ± 0.71	3.95 ± 0.63	8.80 ± 1.97*	8.26 ± 1.32*	4.11 ± 0.51
Segment shortening (%)	7	15.0 ± 4.7	11.6 ± 3.1	12.8 ± 2.2	11.9 ± 2.8	14.0 ± 2.6	10.0 ± 1.6

Mean ± SEM data.
*Significantly different ($P < 0.05$) from the conscious state.

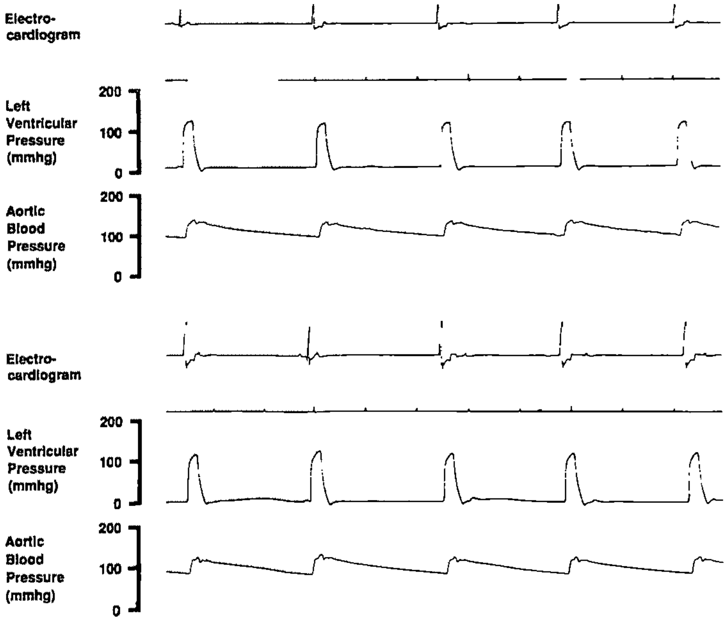


Figure 4. Electrocardiogram and left ventricular and aortic pressure traces from two dogs after sufentanil (25 μg/kg) after pretreatment with 1 mg/kg propranolol and 0.3 mg/kg diltiazem (Experiment C). Note the profound bradycardia with a sinus arrhythmia and junctional escape beats.

Experiment D: Hemodynamic alterations produced by sufentanil and vecuronium after propranolol and diltiazem pretreatment. Pretreatment with propranolol and diltiazem produced hemodynamic alterations similar to those observed in Experiments B and C (Table 4). Administration of vecuronium (0.1 mg/kg) with sufentanil (Table 4) produced similar hemodynamic changes to those observed with sufentanil (25 μg/kg) alone (Experiment C). A significant reduction in heart rate (76 ± 3 to 32 ± 2 beats/min) (Figure 1) occurred. Four of eleven animals developed sinus bradycardia, whereas in seven animals a predominant junctional rhythm with a rare conducted sinus beat was observed (Figure 5). One animal with sinus bradycardia and one with a slow junctional rhythm developed asystole. Each responded to brief chest compression and atropine sulfate (0.4 mg IV) with a sinus bradycardia. Despite the profound negative chronotropic and inotropic state produced by sufentanil, blood pressure was well maintained (Figure 2) and the rate-pressure product was significantly reduced. Left ventricular end-diastolic pressure was significantly

Table 4. Hemodynamic Actions of Sufentaniland Vecuronium (0.1 mg/kg) After Pretreatment With Propranolol (1.0 mg/kg) and Diltiazem (0.3 mg/kg) in Chronically Instrumented Dogs

	N	Conscious	Propranolol (1 mg/kg)	Diltiazem (0.3 mg/kg)	Sufentanil (25 μg/kg) + Vecuronium (0.1 mg/kg)	Naloxone (0.2 mg/kg)
Heart rate-systolic pressure product (beats/min × mm Hg × 10^3)	11	9.0 ± 0.4	9.3 ± 0.4	10.2 ± 0.6	4.2 ± 0.2*	16.7 ± 1.3*
Left ventricular systolic pressure (mm Hg)	10	116 ± 3	116 ± 3	119 ± 3	130 ± 4	160 ± 6*
Left ventricular end diastolic pressure (mm Hg)	10	10 ± 0.8	13 ± 0.8	13 ± 0.9	19 ± 1.2*	22 ± 3.1*
+dP/dt (mm Hg/sec)	10	2529 ± 131	2175 ± 100*	2183 ± 112*	1912 ± 140*	2282 ± 185*
Diastolic coronary blood flow velocity (Hz × 10^2)	9	45 ± 5	49 ± 6	58 ± 8*	40 ± 5	60 ± 10*
Mean coronary blood flow velocity (Hz × 10^2)	9	25 ± 3	28 ± 3	31 ± 5	19 ± 2	35 ± 5*
Diastolic coronary vascular resistance (ru)	9	2.52 ± 0.29	2.30 ± 0.29	1.95 ± 0.21	2.76 ± 0.49	2.79 ± 0.31
Mean coronary vascular resistance (ru)	9	4.40 ± 0.44	3.96 ± 0.44	3.77 ± 0.45	5.96 ± 1.07*	4.66 ± 0.47
Segment shortening (%)	7	19.6 ± 0.8	18.2 ± 1.1	18.4 ± 1.0	14.6 ± 0.9*	12.3 ± 1.1*

Mean ± SEM data.
*Significantly different ($P < 0.05$) from the conscious state.

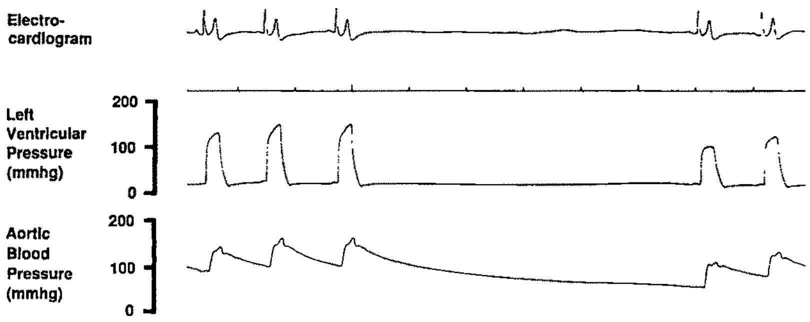


Figure 5. Electrocardiogram and left ventricular and aortic pressure traces after administration of sufentanil (25 μg/kg) and vecuronium (0.1 mg/kg) after pretreatment with propranolol (1 mg/kg) and diltiazem (0.3 mg/kg) (Experiment D). Note the slow sinus bradycardia and 6-second period of asystole with resumption of a sinus bradycardia spontaneously.

elevated to 19 ± 1 mm Hg. Administration of naloxone (0.2 mg/kg IV and 0.2 mg/kg IM) and neuromuscular reversal with neostigmine (0.05 mg/kg) and glycopyrolate (7.0 g/kg) produced hemodynamic alterations (Table 4) similar to those observed with naloxone alone (Experiments A, B, C).

Discussion

Since the initial reports of "high dose" morphine as a suitable anesthetic for patients with compromised cardiovascular function (13), narcotic techniques, including the more recent use of agents such as fentanyl and sufentanil (4,14,15) have been proposed as useful for patients with coronary artery disease. Such techniques result in hemodynamic stability with low heart rates and are believed to maximize coronary perfusion while minimally disrupting the balance between myocardial oxygen supply and demand. In comparisons of fentanyl or sufentanil with other narcotics, fewer hemodynamic alterations were observed with the former agents (16,17). Controversy exists, however, as to which agent is most beneficial. Cardiovascular stability has been claimed to be better with sufentanil than with fentanyl (14,15), but this has not been confirmed in other studies (16,18).

A decrease in heart rate is usually observed after administration of most narcotics, except meperidine. The mechanism of the bradycardia induced by the narcotic agonists is incompletely understood. A centrally mediated increase in parasympathetic tone (19), direct negative chronotropic action at the sinus node (20), potentiation of vagally released acetylcholine at the sinus node (20), and/or reduction in sympathetic activity (19) have all been implicated. Additionally, narcotics depress atrioventricular conduction (21), while also prolonging atrioventricular nodal and ventricular refractory periods (22).

The magnitude of narcotic-induced bradycardia is minimized by slow rates of injection. Several recent reports, however, have described bradycardia and asystole after the administration of sufentanil and vecuronium (6,7) or fentanyl and pancuronium (8). In these reports, all patients had previously received beta-blocking agents alone or with calcium channel blockers. The potential for adverse interaction perioperatively of such combination therapy has been described (9). A clinical report (23) documented four cases of sudden hypotension on induction with sufentanil (2.7–22.7 μg/kg) after sedation with the benzodiazepine lorazepam. Systolic arterial pressures decreased to 60 to 88 mm Hg with heart rates of 48 to 78 beats/min. The lowest heart rate associated with hypotension was in a patient whose preoperative medications included propranolol and verapamil. Although hypotension was not observed in the present study, the profound bradyarrhythmias produced by sufentanil, particularly after pretreatment with diltiazem and propranolol, documents the potential deleterious nature of such pharmacological combination.

The dog differs substantially from humans in the autonomic innervation of the heart. The parasympathetic-sympathetic innervation is extensively interconnected. In contrast, in the human both the vagi and sympathetic innervation are essentially anatomically and physiologically distinct (24). Additionally, the dog appears to possess more predominant parasympathetic tone and responds more profoundly to vagal stimulation. Vagal activation with consequent release of acetylcholine reduces the sinus nodal discharge by decreasing the calcium current and increasing potassium conductance with consequent membrane hyperpolarization and sinus bradycardia (24). In the presence of a severe sinus bradycardia or a block of impulses generated proximal to the atrioventricular (AV) node, the AV junction is capable of initiating a sustained junctional escape rhythm at slow rates that often increase and assume a regular pattern. In 18 of 36 experiments, the dogs responded to administration of sufentanil with slow junctional rhythms. Parasympathetic dominance in the dog, in combination with the ability of narcotics to depress sinus node function, may have resulted in significant slowing of nodal discharge, allowing the development of a junctional escape rhythm. Because humans have different innervation patterns, conduction disturbances might be diminished in comparison to responses in the dog.

Diltiazem has been shown to depress global left ventricular function during volatile anesthesia (25). Furthermore, prolongation of the PR interval and development of second degree heart block with subsequent junctional rhythm have occurred during enflurane (25) and halothane anesthesia (26). Diltiazem acts on the sinoatrial node to decrease the amplitude and rate of rise of the action potential arising from the node. Diltiazem also reduces the slope of diastolic depolarization and suppresses the frequency of spontaneous firing in the excised rabbit sinoatrial node preparation as well as prolonging AV nodal conduction (27).

Generally, negative chronotropic and dromotropic actions of diltiazem, with resultant bradycardia, are more evident under anesthesia than in the conscious state (25–28). It has been suggested that, in the conscious state, sympathetic reflex buffering secondary to peripheral vasodilation produced by the calcium channel blocking agents blunt their direct cardiac effects on inward calcium flux (28). However, because of a decrease in sympathetic tone and reflex sympathetic activity, as well as a direct myocardial depressant action produced by the volatile anesthetics, the potential for drug-induced bradycardia produced by the calcium channel blocking agents is enhanced. Because the narcotics increase vagal and diminish sympathetic tone, as well as directly affecting myocardial conduction, administration of calcium channel blocking agents may result in potentially serious bradyarrhythmias, as demonstrated in the present study.

Previous studies have demonstrated the efficacy of the combination of calcium channel and beta-adrenergic blockade in the treatment of ischemic heart disease (1–3). However, the potential for deleterious interactions of this combination, including diltiazem and propranolol, are well documented (29,30). The occurrence of severe bradycardia and second or third degree heart block with hemodynamic compromise has been reported (29,30).

In this study, both propranolol and diltiazem were administered utilizing a single, intravenous, acute dosage. However, patients who present for surgery usually are on a chronic oral maintenance regime of these agents. Previous studies have documented similar actions of beta-blockers on ischemic myocardial function after chronic (31) or acute administration (32). However, the acute administration of propranolol and/or diltiazem employed in the present investigation may not accurately predict the potential toxicity after chronic administration and may represent a limitation of the present study.

Vecuronium, the monoquaternary analog of pancuronium, has been reported to produce minimal hemodynamic changes when utilized to produce neuromuscular blockade. Booij et al. (33) and Marshall et al. (34) gave doses of vecuronium 3–20 times greater than the effective neuromuscular blocking dose to dogs and cats and found no hemodynamic effects. In clinical studies (35), high doses of vecuronium have also produced insignificant perturbations in cardiovascular homeostasis. Gregoretti et al. (35) concluded that the lack of vagolytic effect of vecuronium may allow other agents such as narcotic agonists to reduce heart rate to a greater extent than when pancuronium is utilized.

The common use of pancuronium in combination with narcotic agonists during cardiac surgery may be ascribed to the ability of this neuromuscular blocking agent to antagonize the central bradycardia induced by the narcotics (36). However, this combination has also been reported to produce ECG changes consistent with myocardial ischemia (36) and has been associated with myocardial lactate production (37) in patients undergoing coronary ravascularization surgery. The tachycardia produced by pancuronium may be mediated through direct cardiac muscarinic (M_2) blockage (38), an increase in cardiac sympathetic activity by potentiating release (38) and inhibiting noradrenergic reuptake (39), and/or potentiation of sympathetic ganglionic transmission (40). Vecuronium is devoid of these actions and, therefore, bradycardia (41) after the combination of narcotic agonists and vecuronium (42) may be more common than when pancuronium is utilized.

The increases in heart rate, arterial pressure, and left ventricular indexes of contractility produced in the present study by naloxone in all experiments is consistent with previous reports (43) of cardiovascular stimulation after reversal of narcotic or balanced anesthesia. Naloxone, in the absence of narcotization, has minimal effects on hemodynamics in conscious or anesthetized animals (44). The production of major cardiovascular stimulation after narcotics has been attributed to an increase in sympathetic discharge (45), an increase in central noradrenergic neuronal activity (46), and/or an increase in circulating catecholamines (45).

Adverse reactions have also been observed clinically during naloxone reversal of narcotic narcosis and include hypertension, acute pulmonary edema, ventricular irritability, and death (47–48). In the present investigation, naloxone increased systemic pressure, produced sinus tachycardia, and elevated left ventricular end diastolic pressure in all experiments, despite pretreatment with beta-blocking and calcium channel blocking agents. Because all experiments were conducted in chronically implanted animals, without nociceptive input or baseline anesthetic to alter endogenous neurovascular tone, the ability of naloxone to produce cardiovascular stimulation after narcotic administration is consistent with a central and/or peripheral mediated increase in sympathetic tone (45). Additionally, there was a greater increase in heart rate with decreased indexes of left ventricular contractility and an increase in left ventricular end-diastolic pressure in experiments B, C, and D compared with experiment A, which may reflect a central interaction of sufentanil, propranolol, and naloxone on cardiovascular control centers (19,46).

The choice of a nondepolarizing neuromuscular relaxant to be used in combination with a high dose narcotic anesthetic technique in patients with ischemic heart disease may be difficult. This study demonstrates the ability of sufentanil to produce profound bradyarrhythmias, particularly after beta-adrenergic and calcium channel blockade. Although the bradyarrhythmias were of greatest magnitude with the combination of sufentanil and vecuronium, previous evidence supports the concept that this result was not due to drug interaction but rather a lack of vagolytic activity of vecuronium. Despite the bradyarrhythmias observed in chronically instrumented dogs, hemodynamic stability was maintained with minimal decreases in arterial or left ventricular pressures. In contrast, in patients with coronary artery or valvular heart disease, such reductions in heart rate may be associated with hemodynamic instability and represent a potentially deleterious clinical situation.

We gratefully acknowledge the excellent technical assistance of John Tessmer and David Schwabe and thank Tamatha Steward and Carol Knapp for the preparation of the manuscript. We are indebted to Janssen Pharmaceuticals for the gracious supply of sufentanil.

References

1. Dargie HJ, Lynch PG, Krikler DM, Harris L, Krikler S. Nifedipine and propranolol: a beneficial drug interaction. Am J Med 1981;71:676–82.
2. Strauss WE, Parisi AF. Superiority of combined diltiazem and propranolol therapy for angina pectoris. Circulation 1985;71: 951–7.
3. Krikler DM, Harris L, Rowland E. Calcium-channel blockers and beta blockers: advantages and disadvantages of combination therapy in chronic stable angina pectoris. Am Heart J. 1982;104:702–8.
4. Lowenstein E, Philbin DM. Narcotic "anesthesia in the eighties." Anesthesiology 1981;55:195–7.
5. Sonntag H, Larsen R. Cardiovascular actions of narcotic analgesics. In: Altura BM, Halevy S, eds. Cardiovascular Actions of

Anesthetics and Drugs Used in Anesthesia. Basal: Karger, 1986:74–102.

6. Starr NJ, Sethna DH, Estafanous FG. Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. Anesthesiology 1986;64:521–3.
7. Schmeling WT, Bernstein JS, Vucins EJ, Cody R. Persistent bradycardia with episodic sinus arrest after sufentanil and vecuronium administration successfully treated with isoproterenol. J Cardiothoracic Anesth (in press).
8. Hartwell BL, Mark JB. Combinations of β-blockers and calcium channel blockers: a cause of malignant perioperative conduction disturbances? Anesth Analg 1986;65:905–7.
9. Sullivan KB, Kapur PA. The effect of β-adrenergic blockade on the cardiovascular response to diltiazem or verapamil in dogs. Anesth Analg 1986;65:1099–1106.
10. Vatner SF. Effects of anesthesia on cardiovascular control mechanisms. Environ Health Perspect 1978;26:193–206.
11. Theroux P, Franklin D, Ross J Jr, Kemper WS. Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. Circ Res 1974;35:896–908.
12. Wilkison DM, Preuss KC, Warltier DC. A microcomputer-based package for determination of regional and global cardiac function and coronary hemodynamics. J Pharmacol Methods 1984;12:59–67.
13. Lowenstein E, Hallowell P, Levine FH, Daggett WM, Austen WG, Laver MB. Cardiovascular responses to large doses of intravenous morphine in man. N Engl J Med 1969;281:1389–93.
14. Sebel PS, Bovil JG. Cardiovascular effects of sufentanil anesthesia. Anesth Analg 1982;61:115–9.
15. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology 1982;56:112–8.
16. Ghoneim MM, Dhanaraj J, Choi WW. Comparison of four opioid analgesics as supplements to nitrous oxide anesthesia. Anesth Analg 1984;63:405–12.
17. Eriksen J, Berthelsen P, Ahn NC, Rasmussen JP. Early response in central haemodynamics to high doses of sufentanil or morphine in dogs. Acta Anaesthesiol Scand 1981;25:33–8.
18. Rosow CE, Philbin DM, Moss J, Keegan CR, Schneider RC. Sufentanil vs fentanyl: ± Suppression of hemodynamic responses. Anesthesiology 1983;59:A323.
19. Laubie M, Schmitt H, Canellas J, Roquebert J, Demichel P. Centrally mediated bradycardia and hypotension induced by narcotic analgesic dextromoramide and fentanyl. Eur J Pharmacol 1974;28:66–75.
20. Loeb JM, Lichtenthal PR, deTarnowsky JM. Parasympathomimetic effects of fentanyl on the canine sinus node. J Auton Nerv Syst 1984;11:91–4.
21. EdSilva RA, Verrier RL, Lown B. Protective effect of the vagotanic action of morphine sulfate on ventricular vulnerability. Cardiovasc Res 1978;12:167–72.
22. Royster RL, Keeler DK, Haisty WK, Johnston WE, Prough DS. Cardiac electrophysiologic effects of fentanyl and combinations of fentanyl and neuromuscular relaxants in pentobarbital-anesthetized dogs. Anesth Analg 1988;67:15–20.
23. Spiess BD, Sathnoff RH, el-Ganzouri AR, Ivankovich AD. High-dose sufentanil: four cases of sudden hypotension on induction. Anesth Analg 65:703–5.
24. Randall WC, ed. Neural Regulation of the Heart. New York: Oxford University Press, 1977:15–129.
25. Kapur PA, Campos JH, Buchea OC. Plasma diltiazem levels, cardiovascular function and coronary hemodynamics during enflurane anesthesia in the dog. Anesth Analg 1986;65:918–24.
26. Kates RA, Zaggy AP, Norfleet EA, Heath KR. Comparative cardiovascular effects of verapamil, nifedipine and diltiazem during halothane anesthesia in swine. Anesthesiology 1984;61: 10–8.
27. Kawai C, Konishi T, Matsuyama E, Okazaki H. Comparative effects of three calcium antagonists, diltiazem, verapamil and nifedipine on the sinoatrial and atrioventricular nodes. Circulation 1981;63:1035–42.
28. Newman RK, Bishop VS, Peterson DF, Leroux EJ, Horwitz LD. Effect of verapamil on left ventricular performance in conscious dogs. J Pharmacol Exp Ther 1977;201:723–30.
29. Sullivan KB, Kapur PA. The effect of β-adrenergic blockade on the cardiovascular response to diltiazem or verapamil in dogs. Anesth Analg 1986;65:1099–106.
30. Reves JG, Kissin I, Lell WA, Tosone S. Calcium entry blockers: uses and implications for anesthesiologists. Anesthesiology 1982;57:504–18.
31. Al-Wathiqui M, Farber N, Pelc L, Gross GJ, Brooks HL, Warltier DC. Improvement of functional recovery of "stunned' canine myocardium by chronic pretreatment with oral propranolol. Am Heart J 1989 (in press).
32. Lange R, Kloner RA, Braunwald E. Enhancement of functional recovery of "stunned" reperfused myocardium by a new ultrashort-acting beta-blocker. J Am Coll Cardiol 1984;3:545.
33. Booij LHJ Edwards RP, Sohn YJ, Miller RD. Cardiovascular and neuromuscular effects of Org NC 45, pancuronium, metocurine, and d-tubocurarine in dogs. Anesth Analg 1980;59: 26–30.
34. Marshall RJ, McGrath JC, Miller RD, Docherty JR, Lamar LC. Comparison of the cardiovascular actions of Org NC 45 with those produced by other non-depolarizing neuromuscular blocking agents in experimental animals. Br J Anaesth 1980; 52(suppl I):215–325.
35. Gregoretti SM, Sohn YJ, Sia RL. Heart rate and blood pressure changes after ORG NC 45 (vecuronium) and pancuronium during halothane and enflurane anesthesia. Anesthesiology 1982;56:392–5.
36. Thomson IR, Putnins CL. Adverse effects of pancuronium during high-dose fentanyl anesthesia for coronary artery bypass grafting. Anesthesiology 1985;62:708–13.
37. Sonntag H, Larsen R, Hilfikero O, Kettler D, Brockschnieder B. Myocardial blood flow and oxygen consumption during high dose fentanyl anesthesia in patients with coronary artery disease. Anesthesiology 1982;56:417–22.
38. Vercruysse P, Bossuyt P, Hanegreefs G, Verbeuren TJ, Vanhoutte PM. Gallamine and pancuronium inhibit pre- and post-junctional muscarine receptors in canine saphenous veins. J Pharmacol Exp Ther 1979;209:225–30.
39. Salt PJ, Barnes PK, Conway CM. Inhibition of neuronal uptake of noradrenalin in the isolated perfused rat heart by pancuronium and its homologues ORG 6368, ORG 7268 and ORG NC 45. Br J Anaesth 1980;52:313–7.
40. Gardier RW, Tsevdos EJ, Jackson DB, Delaunoisal AL. Distinct muscarinic mediation of suspected dopaminergic activity in sympathetic ganglion. Fed Proc 1978;37:2422–8.
41. Durant NN, Marshall IG, Savage DS, Nelson DJ, Sleigh T, Carlyle IC The neuromuscular and autonomic blocking activities of pancuronium, ORG NC45 and other pancuronium analogues in the cat. J Pharm Pharmacol 1979;31:831–6.
42. Marshall RJ, Ojewole JAO. Comparison of the autonomic effects of some currently used neuromuscular blocking agents (proceedings). Br J Pharmacol 1979;66:77P–8P.
43. Desmonts JM, Bohm G, Couderc E. Hemodynamic responses to low doses of naloxone after narcotic-nitrous oxide anesthesia. Anesthesiology 1978;49:12–6.
44. Rutter PC, Potocnik SJ, Ludbrook JL. Factors influencing the effects of intravenous naloxone on arterial pressure and heart rate after haemorrhage in conscious rabbits. Clin Exp Pharmacol Physio 1986;13:383–97.

45. Flacke JW, Flacke WE, Bloor BC, Olewine S. Effects of fentanyl, naloxone, and clonidine on hemodynamics and plasma catecholamine levels in dogs. Anesth Analg 1983;62:305–13.

46. Laverty R, Roth RH. Clonidine reverses the increased norepinephrine turnover during morphine withdrawal in rats. Brain Res 1980;182:482–5.

47. Flacke JW, Flacke WE, Williams GD. Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. Anesthesiology 1977;47:376–8.

48. Michaelis LL, Hickey PR, Clark TA, Dixon WM. Ventricular irritability associated with the use of naloxone hydrochloride. Two case reports and laboratory assessment of the effect of the drug on cardiac excitability. Ann Thorac Surg 1974;18:608–14.

Fifty-Seven Years Ago in
Anesthesia & Analgesia

D. A. Wood: Survey of anesthesia given in 550 brain operations in the years 1921 to 1930 inclusive. Current Researches in Anesthesia and Analgesia: 1932;11:201–5.

Today's anesthesiologist should read this paper to really understand how far we have come and also how clinically astute and skillful our predecessors could be. In this article, Dr. Wood recounts her experience in handling 550 anesthetics for cranial neurosurgical procedures in 433 patients at the University of California Medical School and Hospital in San Francisco in the nine years between 1921 and 1930. The patients ranged in age from three days (46 were under three years old) to 79 years (13 were 70 to 79 years old). Craniotomies at the time were being performed mainly with local anesthesia in most institutions in North America, but in Dr. Wood's series there were no patients in whom local anesthesia was used, except for 20 cases started with local that proved so unsatisfactory that ether anesthesia had to be induced intraoperatively. Nitrous oxide was also not used in these 550 cases. N_2O increased intracranial pressure, Dr. Wood said, when cyanosis developed, and cyanosis was certainly not unheard of when N_2O was used in the 1920s. All 550 anesthetics were ether anesthetics. Premedication consisted of small doses of oral barbiturates, rarely morphine, but often only atropine. Induction of anesthesia was with open-drop ether. Intravenous amorbarbital (Amytal), recently introduced, was tried in three cases as the primary anesthetic but then abandoned because the patients kept waking up. Intravenous amobarbital was also tried in small amounts before open-drop ether was given, but this too was abandoned on the basis that it was considered unnecessary if premedication with oral barbiturates had been used. Anesthesia was maintained by insufflating ether vapor (apparently in air) through a metal pharyngeal airway that helped prevent soft tissue obstruction of the airway. The positions in which surgery was performed included sitting bolt upright (in a dental chair), supine, lateral or prone with the head supported by a padded horse-shoe shaped headrest (the author fails to mention this latter position usually required that the anesthetist sit on the floor under the head of the table to observe eye-signs, lift the chin if the airway became obstructed, etc.). Hemostasis was achieved with electrocautery. No explosions, though. The concentration of ether in the operative field never got to the lower limit of flammability because of the barrier created by surgical drapes and the fact that ether, being heavier than air, gravitated to the floor, not to the operative area. Hypodermoclysis with Ringer's solution, not IV, provided hydration. In an emergency, e.g., hemorrhagic shock, 500 mL of Ringer's solution "or blood transfusions when available" were given. A total of 16 blood transfusions were given in the 550 cases. Operations included 108 excisions of tumors (many in the posterior fossa), 24 temporal decompressions, 54 Gasserian ganglionectomies, 13 transsphenoidal hypophysectomies, and 14 drainages of brain abscesses. Intraoperative increases in intracranial pressure were handled by ventricular puncture (especially useful with posterior fossa tumors) or 50–75 mL of hypertonic 25% Ringer's solution injected intravenously. Emphasis was placed on the need for gentle transfer of the patient from the operating room table to the bed at the conclusion of surgery. No data are given on intraoperative mortality. Postoperative morbidity and mortality ascribed to anesthesia involved three cases of parotitis, three of bronchitis, three of pneumonia (one death), one case of "cardiac dilatation" (fatal), and one case of lung abscess (fatal).

ANESTH ANALG
1989;69:15–20

Spinal Cord Transmission of Impulses during High Spinal Anesthesia as Measured by Cortical Evoked Potentials

Eberhard Lang, MD, Joerg U. Krainick, MD, and Hans U. Gerbershagen, MD

LANG E, KRAINICK JU, GERBERSHAGEN HU. Spinal cord transmission of impulses during high spinal anesthesia as measured by cortical evoked potentials. Anesth Analg 1989;69:15–20.

Cortical evoked potentials (CEPs) resulting from posterior tibial nerve stimulation could be recorded before, but not during, diagnostic high spinal anesthesia to T2–3 in six patients with chronic pain. In contrast, spinal cord stimulation at T8–9 during high spinal anesthesia resulted in CEPs with reduced peak amplitudes and increased P1 and N2 latencies. Amplitudes of the CEPs evoked by spinal cord stimulation increased with increases in stimulus intensity before and during high spinal anesthesia (N = 3). During spinal anesthesia, higher stimulus intensities were required to evoke CEPs of similar amplitudes as before. Because CEPs evoked by stimulation of the posterior tibial nerve disappeared, but those evoked by spinal cord stimulation did not, it is concluded that spinal anesthesia is a result of blockade of nerve roots, not blockade of neural transmission within the cord. Therefore, diagnostic high spinal anesthesia cannot exclude an origin of pain within the spinal cord.

Key Words: ANESTHETIC TECHNIQUES, SPINAL. BRAIN, EVOKED POTENTIALS.

Anesthesia after subarachnoid administration of local anesthetic is generally considered to result from blockade of the spinal nerve roots and dorsal root ganglia (1–4). Penetration of local anesthetic into the outer parts of the spinal cord has been suggested on clinical grounds (2,5,6), and it has been shown radioautographically in animals (7–10). However, the extent of penetration into the spinal cord of local anesthetics in concentrations adequate to block neuronal conduction is unknown (1,11,12).

We used diagnostic high spinal anesthesia (HSA) in patients with chronic pain in the lower half of the body in an attempt to confirm the diagnosis of central pain. To ensure that pain persisting during HSA is not of spinal origin, at a site below the level made anesthetic by HSA, it must be proved that all ascending spinal tracts below the upper level of anesthesia have been blocked. Therefore, we monitored transmission in the spinal cord, before and during HSA by measuring cortical evoked potentials (CEPs) elicited by direct spinal cord stimulation via an epidural electrode. We also measured spinal nerve root block during HSA by measuring CEPs elicited by posterior tibial nerve stimulation.

Methods and Material

Studies were performed on six patients who had given their informed consent. In each patient, an electrode for bipolar spinal cord stimulation (Pisces Quad M 3487, Medtronic) was placed, under x-ray control, in the midline of the dorsal epidural space at the T9 (N = 4) or T8 (N = 2) level (13). CEPs evoked by spinal cord and posterior tibial nerve stimulation were recorded before and during HSA with the electrodiagnostic system Pathfinder I (Nicolet).

Stimulation

Before and during HSA, all patients received bipolar spinal cord stimulation with rectangular monophasic constant current pulses (cathode cranial, stimulus duration 0.2 msec, 3.0 stimuli/sec, current intensity 2–3 times the sensory threshold). In three of the six patients, the current intensity was increased, in steps of approximately 2.5 mA, above the sensory threshold before and 20 to 60 min after the start of HSA. In one of these patients, the stimulus duration was also increased stepwise (0.1 msec) from 0.2 msec up to 1.0 msec at 30 mA during HSA. The quality and localization of stimulus sensation were noted.

Both tibial nerves were stimulated behind the ankles via bipolar surface electrodes (stimulus duration 0.2 msec, 3.0 stimuli/sec, current intensity at 4 mA above motor threshold).

Received from the Deutsches Rotes Kreuz-Schmerzzentrum Mainz, Mainz, Federal Republic of Germany. Accepted for publication December 20, 1988.

Address correspondence to Dr. Lang, Institut für Physiologie und Biokybernetik, University of Erlangen, Universitätsstr. 17, D-8520 Erlangen, Federal Republic of Germany.

©1989 by the International Anesthesia Research Society

Table 1. Patient Data

Case No.	Age (yrs)	Sex	Height (cm)	Previous Spine Surgery	Neurological Deficit	Pain Area
1	51	M	165	Spondylodesis L3–S1, 3 times	Allodynia left lateral thigh	Low back, both legs
2	51	M	172	None	None	Both popliteal fossae
3	50	F	173	DREZ lesion and rhizotomy D8–10 left	Hypaesthesia D8–L3 left, foot extensor paresis left, ataxia	Left buttock, thigh, and lower abdomen
4	42	F	154	None	None	Left middle abdomen
5	25	F	177	None	None	Left buttock
6	57	M	172	None	Conus lesion, hypaesthesia below L2, bladder and anal sphincter disturbances	Low back

Table 2. Current Intensities of Spinal Cord Stimulation at Sensation Threshold Before and During HSA

Case No.	Current (mA) Before HSA	Current (mA) During HSA
1	5.0	12.0
2	6.0	14.6
3	4.0	7.0
4	6.0	11.2
5	5.5	16.2*
6	4.2	12.9

*The stimulus duration was 0.8 msec, in all other measurements 0.2 msec.

Recordings

CEPs evoked by spinal cord and posterior tibial nerve stimulation were recorded from Ag/AgCl surface electrodes placed in positions Cz′ and Fpz as reference (10–20 system). The signals from the scalp electrodes were filtered (bandpass 5–250 Hz), averaged (32–250 stimulus responses), and recorded in the 130 or 150 msec after stimulus onset.

The signals were stored on disk for off-line measurement of peak latencies and peak to peak amplitudes. The peaks of the CEPs resulting from spinal cord stimulation were labeled consecutively, with use of N1–N3 for the first 3 negative (upward) deflections and P1–P3 for the first three positive (downward) deflections.

High Spinal Anesthesia

The patients were not premedicated. The cardiovascular system was monitored continuously by electrocardiograph (ECG) and oscillometric blood pressure measurements (Dinamap, Critikon). After infusion of 1,500-mL electrolyte solution and intravenous injection of 0.5 mg atropine sulfate, HSA was induced.

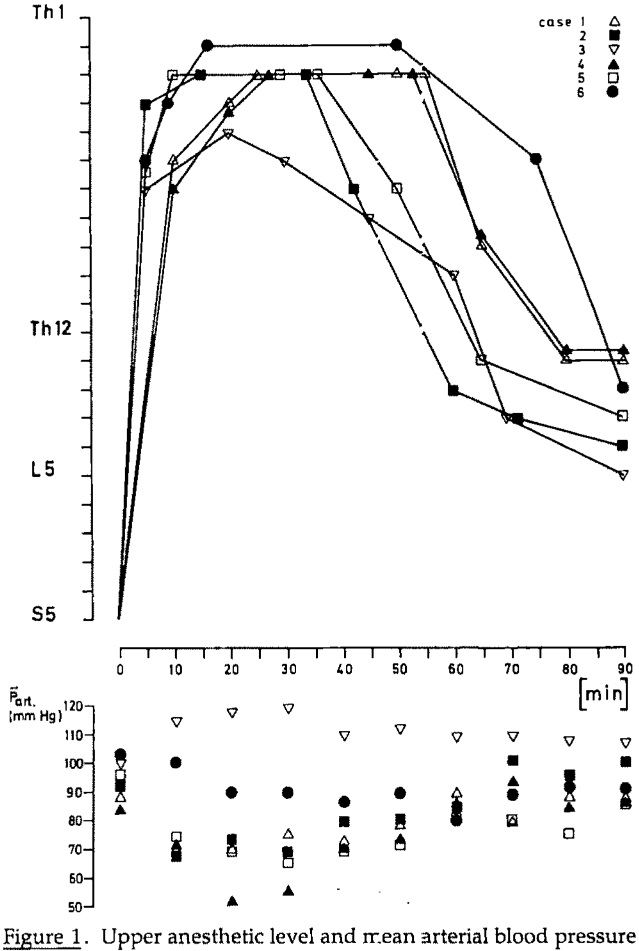


Figure 1. Upper anesthetic level and mean arterial blood pressure after lumbar subarachnoid injection of 100 mg articain. Different symbols represent data in six patients.

In the right lateral recumbent and 5° Trendelenburg position, 2 mL of hyperbaric articain 5% (Ultracain, Hoechst) was injected through a 25-gauge spinal needle into the subarachnoid space at L_{3-4} (N = 4) or L_{4-5} (N = 2). Patients were then turned into the supine position, and the level of anesthesia was achieved by changing the degree of the head-down tilt of the operating table (T3, N = 4; T2, N = 1; T5, N = 1). The extent of neuronal blockade was determined by frequent measurements of touch, pin

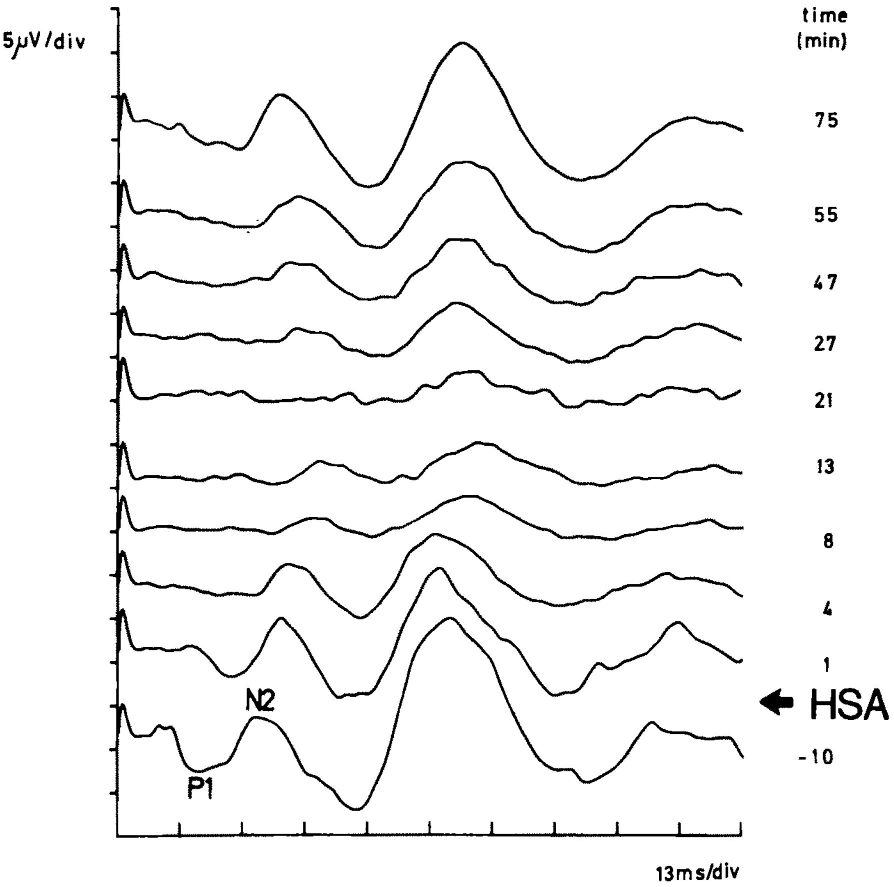


Figure 2. CEPs evoked by spinal cord stimulation (T8) with constant stimulus parameters before and during HSA in a representative patient (Case 1).

prick and cold sensation in the dermatomes of spinal segments S5–C2, vibratory sensation at the malleoli, patellae, iliac crests, ribs and sternum, proprioception in the toes, knees, and hips, and motor function of the lower extremities.

Statistical Analysis

The P1 and N2 latencies of the CEPs after spinal cord stimulation were evaluated statistically by the Wilcoxon matched pairs signed rank test. $P < 0.05$ was considered statistically significant.

Results

Control Measurements Before High Spinal Anesthesia

Patient data are summarized in Table 1. In all patients, CEPs elicited by posterior tibial nerve stimulation were normal. Spinal cord stimulation (3.0 Hz) was felt above sensory threshold intensity (Table 2) as throbbing in the lower abdomen and in both legs. The intensity of sensation increased as the stimulus current intensity increased until it became a strong and unpleasant throbbing, at which point stimulation ceased.

As the current intensity of spinal cord stimulation increased (N = 3), the amplitudes of all CEP peaks increased (Figures 4A and 5A). Peak latencies did not change.

Measurements During High Spinal Anesthesia

Anesthetic levels and mean arterial blood pressures are shown in Figure 1. The maximal decrease in mean blood pressure averaged 21%. Below the highest level of sensory blockade, all sensory and motor functions tested were abolished. Chronic pain was completely relieved by HSA in only one of the patients (Case 6). Repeated stimulation of both tibial nerves produced no sensation and no CEPs in any patient until regression of anesthesia from upper thoracic levels occurred.

Spinal anesthesia at levels above T9–8 decreased the intensity of sensation and all peak amplitudes of CEPs produced by spinal cord stimulation (constant stimulus intensity) in each patient (Figures 2 and 3).

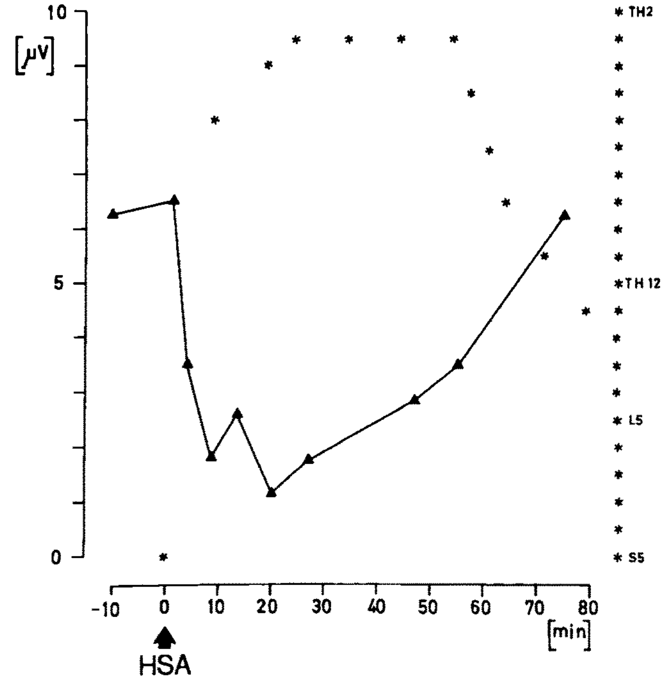


Figure 3. P1-N2 amplitude of CEPs evoked by spinal cord stimulation (▲) and anesthetic level (*) in a representative patient (same patient as in Figure 2).

In two patients, the stimulus intensity was suprathreshold also during HSA, and the CEP amplitudes were smallest 21 and 25 min after subarachnoid injection of the local anesthetic (Figure 3). Thereafter, their amplitudes increased again. In the other four patients, CEPs disappeared at the stimulus intensities used but could be recorded at higher stimulus intensities in each patient.

The sensory threshold was increased in all patients during HSA (Table 2). Above threshold, patients felt a throbbing that was not painful in the lower abdomen and in both legs. If current intensity (N = 3) or stimulus duration (N = 1) was increased, both intensity of stimulus sensation and all peak amplitudes of CEPs increased (Figures 4B and 5B). A comparison of the relationships between stimulus intensity and peak amplitudes of CEPs before (Figure 5A) and during HSA (Figure 5B) showed that higher stimulus intensities were required during HSA.

When CEPs, evoked by spinal cord stimulation with constant stimulus parameters, were maximally decreased in amplitudes during HSA, P1 and N2 latencies increased ($P < 0.05$; N = 6) (Figure 6). Latencies of P1 and N2 did not change significantly when stimulus current intensity was increased.

Discussion

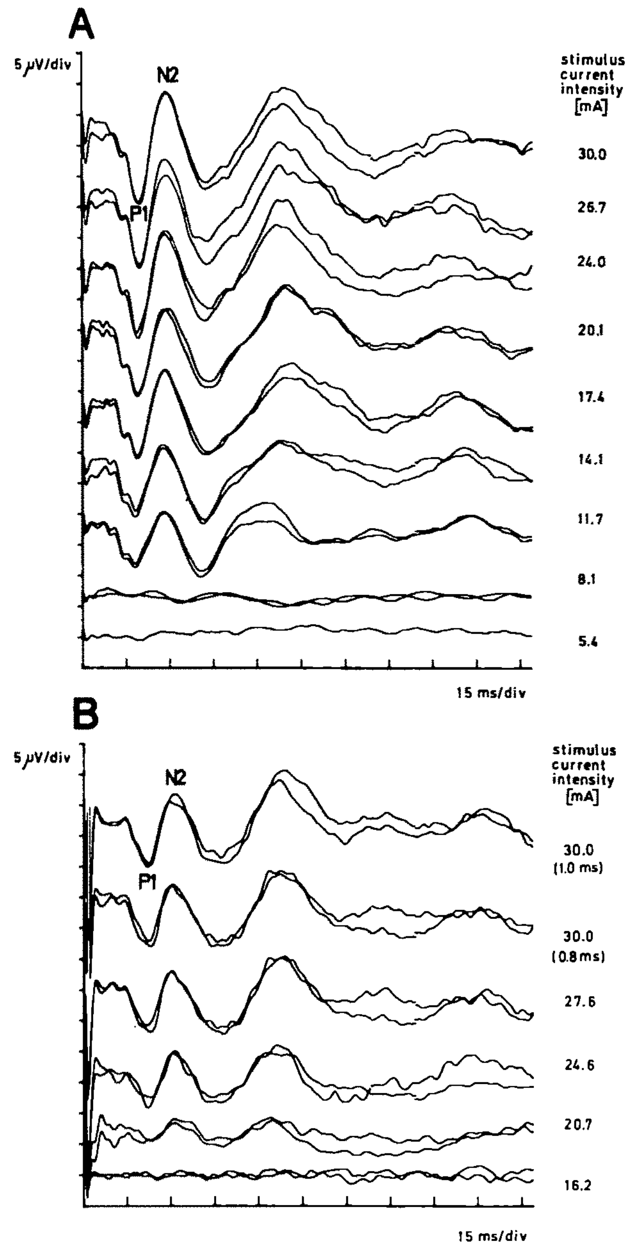


Figure 4. CEPs (double recordings) evoked by spinal cord stimulation. Stepwise increase of stimulus intensities before (A) and during (B) HSA in a representative patient (Case 5). Stimulus duration was 0.2 msec before HSA (A) and 0.8 or 1.0 msec during HSA (B) to give a greater range of stimulation intensity.

In addition to the known effects of local anesthetics on the spinal cord during spinal or epidural anesthesia (1–4,9–12,14), our study showed that, during HSA to T2–3, spinal cord fibers stimulated at the T8–9 level are excitable and are able to conduct impulses at a time when nerve roots below the upper anesthesia level are completely blocked. The loss of sensation by a block of the lumbosacral roots was proved by the absence of CEPs previously evocable by posterior tibial nerve stimulation. This result agrees with other studies in which segmental zones of anesthesia (touch) were not achieved during epidural (15–17) or subarachnoid (18) injection of bupivacaine 0.5% and

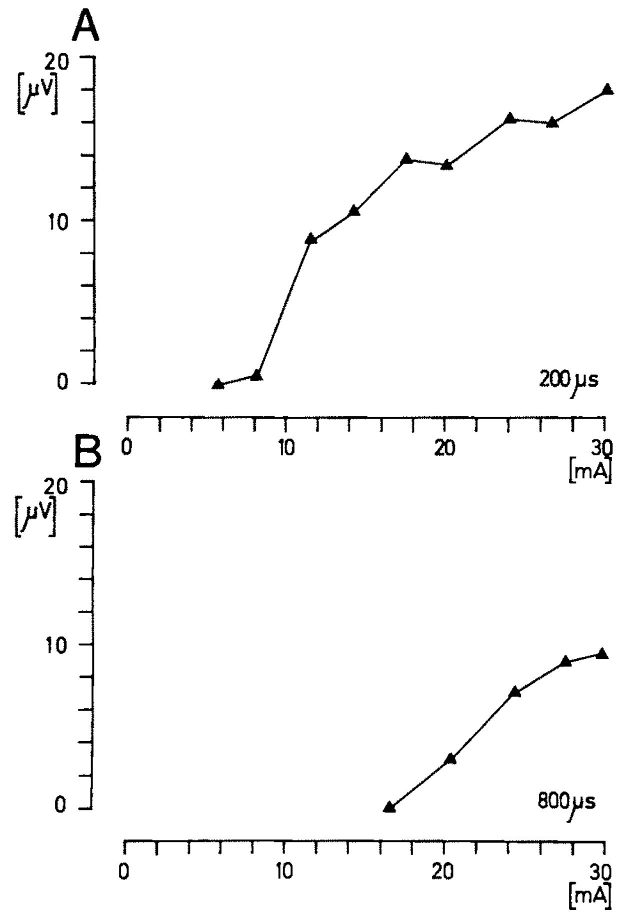


Figure 5. P1-N2 amplitude of CEPs (grand averages of double recordings) versus intensity of spinal cord stimulation before (**A**) and during (**B**) HSA in a representative patient (same patient as in Figure 4).

CEPs after dermatomal or peripheral nerve stimulation could be recorded.

CEPs resulting from spinal cord stimulation have been reported previously (19). As for peripheral nerve stimulation (20), we found that amplitudes of CEPs evoked by spinal cord stimulation were dependent on stimulus intensity. The stimulus intensity determines the size of the electric field and thereby the number of excited spinal cord fibers. Therefore, we used the amplitudes of CEPs after spinal cord stimulation as a possible indicator of changes in the number of excited spinal cord fibers. Another factor that could cause the changes observed (2) would be cerebral depression secondary to hypotension during HSA, but this is unlikely because a relevant reduction of cerebral or spinal cord blood flow is unlikely at the mean arterial blood pressure measured in our patients. Above a mean arterial blood pressure of 40 mm Hg, in animals, changes of cortical (21) and spinal (22) evoked potentials did not occur.

CEP amplitudes decreased during HSA when constant stimulus parameters were used. The changes observed must be due to the effects of distribution and uptake of subarachnoid local anesthetic that induce conduction block of roots and spinal cord fibers that were excited before the administration of local anesthetic.

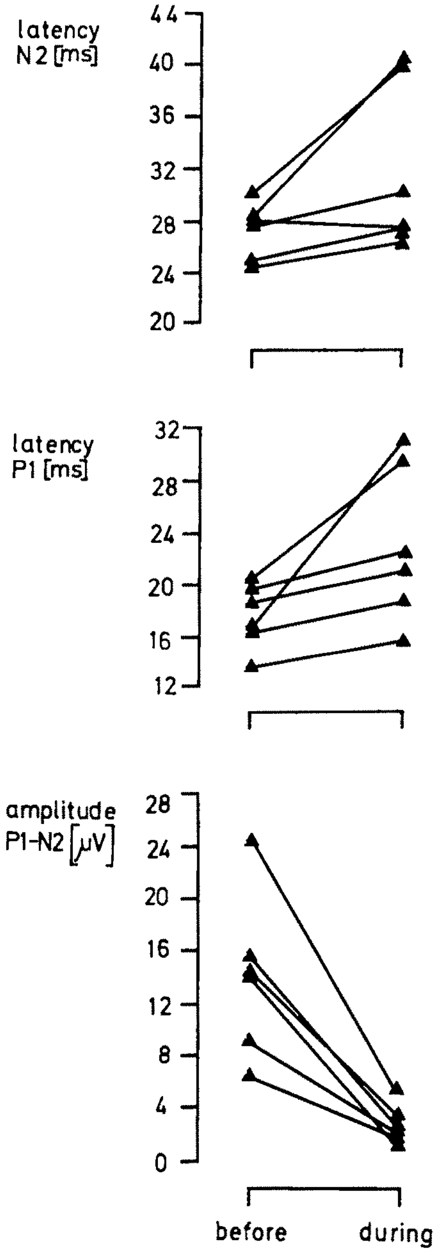


Figure 6. P1 and N2 latencies and P1-N2 amplitudes of CEPs in six patients evoked by spinal cord stimulation (constant stimulus intensity) before and during HSA.

Results in two patients in whom CEP amplitudes were lowest 21 and 25 min after subarachnoid injection of 100 mg articain indicate that the spinal cord was penetrated most deeply by the local anesthetic at that time. A recovery of CEP amplitudes thereafter indicates the elimination of the local anesthetic from the spinal cord. Thus, monitoring of CEPs could possibly be used to measure changes in degree of blockade of the spinal cord, because this cannot be detected clinically by testing the touch sensation after blockade of the spinal nerve roots.

Sensory threshold was increased during HSA. Probably this increase was due to a block of the fibers at the "border" of the spinal cord. It is not known which spinal cord tracts are excited by an epidural electrode close to the dorsal columns, although the dorsal columns are most likely to be involved (13). However, the increase of CEP amplitudes after stepwise increases of stimulus intensity above the sensory threshold indicates the presence of an area within the spinal cord where fibers have not been blocked by the local anesthetic.

The increase of P1 and N2 latencies during HSA, at the time when there were decreases in amplitudes of CEPs resulting from spinal cord stimulation, are in accordance with known effects. Local anesthetics do induce slowing of conduction velocity of nerve fibers before a complete block occurs (23,24). In addition, our data on changes in CEP latencies agree with the findings of others after dermatomal or peripheral nerve stimulation during incomplete local anesthetic block of spinal nerve roots (15,17,18).

It can be concluded that monitoring of CEPs may provide detailed information on the block of the spinal cord by local anesthetics. Using CEPs, we have shown that HSA does not produce a "chemical transection" nor a complete block of all ascending spinal cord fibers. Thus, HSA cannot be used as a diagnostic tool to differentiate between pain originating within the spinal cord below or the central nervous system above the anesthetic level.

References

1. Bridenbaugh PO, Greene NM. Spinal subarachnoid neural blockade. In: Cousins M, Bridenbaugh PO, eds. Neural Blockade in Clinical Anesthesia and Management of Pain. Philadelphia: Lippincott, 1987:212–51.
2. Greene NM. Physiology of Spinal Anesthesia. 3rd ed. Baltimore: Williams & Wilkins, 1981:1–54.
3. Forbes AR, Roizen MF. Does spinal anesthesia anesthetize the spinal cord? Anesthesiology 1978;48:440–5.
4. Frumin MJ, Schwartz H, Burns JJ, Brodie BB, Papper EM. Dorsal root ganglion blockade during threshold segmental spinal anesthesia in man. J Pharmacol Exp Ther 1954;112:387.
5. Bromage PR. Lower limb reflex changes in segmental epidural analgesia. Br J Anaesth 1974;46:504–8.
6. Urban BJ. Clinical observations suggesting a changing site of action during induction and recession of spinal and epidural anesthesia. Anesthesiology 1973;39:496–503.
7. Grodinsky M, Beber M, Baker CP. Test for presence of novocaine in nervous tissue. Science 1933;77:450.
8. Howarth F. Studies with radioactive spinal anaesthetic. Br J Pharmacol 1949;4:333–47.
9. Bromage PR, Joyal AC, Binney JC. Local anesthetic drugs: penetration from the spinal extradural space into the neuraxis. Science 1963;140:392–4.
10. Cohen EN. Distribution of local anesthetic agents in the neuraxis of the dog. Anesthesiology 1968;29:1002–5.
11. Greene NM. Uptake and elimination of local anesthetics during spinal anesthesia. Anesth Analg 1983;62:1013–24.
12. Bromage PR. Mechanism of action of extradural analgesia. Br J Anaesth 1975;47:199–212.
13. Krainick JU, Thoden U. Dorsal column stimulation. In: Wall PD, Melzack R, eds. Textbook of Pain. Edinburgh: Churchill Livingstone, 1984:701–5.
14. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg 1985;64:715–30.
15. Lund C, Selmar P, Hansen OB, Hjortso NC, Kehlet H. Effect of epidural bupivacaine on somatosensory evoked potentials after dermatomal stimulation. Anesth Analg 1987;66:34–8.
16. Lund C, Hansen OB, Mogensen T, Kehlet H. Effect of thoracic epidural bupivacaine on somatosensory evoked potentials after dermatomal stimulation. Anesth Analg 1987;66:731–4.
17. Saugbjerg P, Asoh T, Lund C, Kühl V, Kehlet H. Effects of epidural analgesia on scalp-recorded somatosensory evoked potentials to posterior tibial nerve stimulation. Acta Anaesthesiol Scand 1986;30:400–3.
18. Lund C, Selmar P, Hansen OB, Kehlet H. Effect of intrathecal bupivacaine on somatosensory evoked potentials following dermatomal stimulation. Anesth Analg 1987;66:809–13.
19. Nashold B, Somjen G, Friedman H. Paresthesias and EEG potentials evoked by stimulation of the dorsal funiculi in man. Exp Neurol 1972;36:273–87.
20. Joerg J. Praktische SEP Diagnostik. Stuttgart: Enke, 1983:14.
21. Gregory PC, Mc George AP, Fitch W, Graham DI, Mackenzie ET, Harper AM. Effects of hemorrhagic hypotension on the cerebral circulation. II. Electrocortical function. Stroke 1980; 10:719–23.
22. Hitchon PW, Lobosky JM, Wilkinson TT, Yamada T, Torner JC, Grant PR. Direct spinal cord stimulation and recording in hemorrhagic shock. Neurosurgery 1985;16:796–800.
23. Franz DN, Perry RS. Mechanisms for differential block among single myelinated and non-myelinated axons by procaine. J Physiol 1974;236:193–210.
24. Heavner JE, de Jong RH. Lidocaine blocking concentrations for B- and C- nerve fibres. Anesthesiology 1974;40:228–33.

ANESTH ANALG
1989;69:21–7

Oral Transmucosal Fentanyl Citrate (Lollipop) Premedication in Human Volunteers

Theodore H. Stanley, MD, Brian Hague, BS, David L. Mock, MD, James B. Streisand, MD, Sally Bubbers, MD, Ray R. Dzelzkalns, MD, Peter L. Bailey, MD, Nathan L. Pace, MD, Katherine A. East, MS, and Michael A. Ashburn, MD

STANLEY TH, HAGUE B, MOCK DL, STREISAND JB, BUBBERS S, DZELZKALNS RR, BAILEY PL, PACE NL, EAST KA, ASHBURN MA. Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers. Anesth Analg 1989;69:21–7.

The authors determined whether fentanyl incorporated into a candy lollipop, oral transmucosal fentanyl citrate (OTFC), would cross mucosal tissues of the mouth in sufficient quantities during and after dissolution to produce sedation and/or analgesia. Associated respiratory and circulatory changes, side effects, and plasma concentrations of fentanyl were also measured. The evaluations were done in 28 adult volunteers who received fentanyl citrate in doses of 5, 4, 2, 1, and 0.5 mg in OTFC and rapidly sucked the lollipops (N = 20) or allowed them to passively dissolve (N = 8). Rapid consumption of OTFC resulted in more rapid onset of a pleasant feeling (first subjective sensation) but not more rapid onset of objective sedation or analgesia than passive dissolution. There was a significant correlation between dose of OTFC and magnitude of sedation ($P < 0.001$, Spearman rank correlation = −0.82). Higher doses of OTFC produced greater and longer lasting analgesia and respiratory depression and a higher incidence of nausea and vomiting than lower doses, but pruritus (33%–87%) was not related to the dose of OTFC. Heart rate and arterial blood pressures were not changed by any dose of OTFC. The data indicate that low doses of OTFC (0.5 and 1 mg, equivalent to 5–20 $\mu g \cdot kg^{-1}$ of fentanyl citrate) produce analgesia and sedation with minimal side effects and little respiratory depression in adult volunteers and deserve further evaluation in patients.

Key Words: PREMEDICATION—oral transmucosal. ANALGESICS—fentanyl.

Recent synthesis of potent, highly lipid soluble drugs that can be supplied as water soluble salts have provided the opportunity to explore new administration techniques for premedication (1,2). The citrate salt of fentanyl is soluble in both water and a number of candy matrices, and is resistant to heat (melting point = 152°C) (1,3–5). These properties suggest that fentanyl citrate may be incorporated into a nonthreatening, psychologically appealing delivery system, such as a lollipop (oral transmucosal fentanyl citrate, OTFC), which could be used for premedication before operation. The purpose of this study was to evaluate OTFC premedication in adult human volunteers. Our specific objectives were to determine whether OTFC would cross the mucosal tissues of the mouth in sufficient quantities during and after dissolution to produce sedation and/or analgesia. We also attempted to measure the time of onset, magnitude and duration of sedation and analgesia, associated respiratory and circulatory changes, side effects, and plasma fentanyl concentrations after a variety of doses of OTFC.

Methods

Approval was received from the University of Utah Human Study Committee and the United States Food and Drug Administration, and written, informed consent was obtained from 28 adult volunteers before beginning the study. As OTFC had never been used before, the doses of fentanyl, as well as the number and grouping of volunteers, were not predetermined but incrementally selected according to clinical im-

---

Received from the Department of Anesthesiology, The University of Utah School of Medicine, Salt Lake City, Utah. Accepted for publication February 3, 1989.

Supported in Part by Stanley Research Foundation.

Address correspondence to Dr. Stanley, Department of Anesthesiology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132.

©1989 by the International Anesthesia Research Society

P 24560.

pressions of drug effects. Furthermore, the investigators were not blinded to the dose of fentanyl consumed by each volunteer. It was decided that initial exposures would be with 5 mg of fentanyl citrate to determine if in adults any sedation or analgesia could be obtained from a fentanyl lollipop. As the study progressed, the doses utilized were decreased to 4, 2, 1 mg, and then eventually 0.5 mg. Volunteers were asked to suck actively on the lollipop or allow it to dissolve passively in their mouth.

Lollipops were made by heating a candy base to 150°C and then adding the carefully measured amount of fentanyl citrate crystals (obtained from Janssen Pharmaceutica of Piscataway, N.J.). After mixing, to ensure uniform distribution of the drug, the candy-fentanyl mixture was poured into molds at 107°C, a holder added, and the lollipops allowed to cool and harden before removal from the molds. All lollipops, irrespective of the dose of fentanyl, were the same size, 1.6 cc.

Each volunteer had fasted for at least 8 hr and had abstained from alcohol, smoking, and all other medication for at least 24 hr. On arrival the morning of the study, volunteers were placed in the supine position and had an infusion of normal saline started at a rate of 40 mL/hr in a peripheral vein. They also had a standard blood pressure cuff applied to an upper arm, a Criticare Systems Model 501 pulse oximeter attached to a finger, a standard lead II electrocardiogram started and were evaluated for pain threshold via a Tursky (graded, electrical pain delivering) electrode attached to a forearm (6–8).

Pain threshold was determined using a Grass S88 stimulator and stimulation isolation unit (Grass medical instruments CCU IA) to deliver an electrical stimulus (square wave, 60 Hz) of 0.4 sec duration through a concentric (Tursky) electrode (Farral Instruments) applied to the dorsal nondominant forearm (6–8). The electrode was applied to the skin after shaving the area and preparing it with an abrasive cream. After removing the abrasive cream, electrode contact was insured with a standard conductive gel. If initial current applied was below sensation threshold, the current was increased by 0.2 to 0.5 mAmps every 5 sec until the subject described the current as painful (pain threshold). Three such measurements were taken and averaged at each test time. Maximum allowable current was 32.2 mAmps.

All subjects had baseline pain threshold, systolic arterial blood pressure (SBP), heart rate (HR), oxygen saturation, and respiratory rate (RR) determined following a 15-min equilibration period. In addition, level of consciousness (sedation score) was determined according to the following criteria: 1 = asleep, not readily arousable; 2 = asleep, but arousable; 3 = drowsy; 4 = awake. Volunteers were asked to indicate when they first began to feel sleepy. End-tidal CO_2 ($P_{ET}CO_2$) was measured by allowing each subject (with a nose clip in place) to breathe quietly through a mouthpiece attached to a Beckman LB-2 infrared CO_2 analyzer. Following this, a venous blood sample (5 mL) was obtained for fentanyl plasma analysis.

After collection of baseline data, volunteers were given a fentanyl lollipop and instructed to suck it as fast as possible (N = 20) or to place it in their buccal pouch and allow it to passively dissolve (N = 8). Repeated measurements of all variables were made every 10 min after beginning lollipop consumption and additional venous blood samples were obtained every 20 min during the first hour. Measurements and blood sampling were made every 30 min during the second hour and every hour thereafter for 8 hr. All subjects were questioned every 15 min to determine subjective responses as well as the presence or absence of pruritus, nausea, and headache. Episodes of vomiting were recorded. Volunteers in whom pulse oximeter oxygen saturation decreased to 80% or less for 15 sec or more were instructed to breathe deeply until the reading reached 95% or higher. Subjects with one or more episode of oxygen desaturation (<80%) during the last hour of the study were given naloxone, 0.4 mg IV, in two divided increments. All subjects were instructed not to drive or operate mechanical equipment for 24 hr after the study.

Peripheral venous blood obtained for fentanyl analysis was centrifuged and the plasma removed and frozen at –18°C until time for analysis. Following thawing, fentanyl was extracted from plasma with a mixture of hexane and ethanol (volume ratio 19:1). Plasma fentanyl (concentration expressed as the base) was measured by a capillary gas chromatography-chemical ionization mass spectrometric (CGC/CIMS) method, which employed a Finnegan 4500 gas chromatograph/mass spectrometer linked to a Finnegan INCOS data system (9). Chromatographic separation was achieved using hydrogen as a carrier gas (60–100 $cm \cdot sec^{-1}$) and a DB5-15w column with a 1 μM film thickness. Methane and ammonia were the reagent gases for the mass spectrometer. The full sample was injected and injection temperature was 265°C. Column temperature was programmed at 170°C for 0.5 min and then increased at 23°C/min to 300°C. Transfer line temperature was 230°C and ion chamber temperature 120°C. Carfentanil was used as an internal standard and the current monitored at m/z 337 for fentanyl and m/z 395 for carfentanil. Quantitation

Table 1. Demographic Data of 28 Volunteers Receiving Oral Transmucosal Fentanyl Citrate

	Lollipop Consumption		Fentanyl Citrate in Lollipop (mg)				
	Fast N = 20	Slow N = 8	5 N = 7	4 N = 3	2 N = 8	1 N = 2	0.5 N = 8
Subject Weight (kg)							
Mean	73	69	78	72	71	56	71
SD	±10	±12	±10	±6	±13	±12	±7
Fentanyl Administered (μg/kg)							
Mean	28	48	65	56	29	18	7
SD	±23.3	±19.2	±8.1	±4.8	±5.2	±3.9	±0.7
Female/male	3/17	2/6	0/7	1/2	1/7	1/1	2/6
Active (fast) consumption (N)	—	—	4	2	4	2	8
Passive (slow) consumption (N)	—	—	3	1	4	0	0

Table 2. Delivery and Effect of Oral Transmucosal Fentanyl Citrate in 28 Volunteers

	Lollipop Consumption		Fentanyl Citrate in Lollipop (mg)				
	Fast N = 20	Slow N = 8	5 N = 7	4 N = 3	2 N = 8	1 N = 2	0.5 N = 8
Consumption Time (min)							
Mean	6.0*	43.6	29‡	23‡	17.9‡	7.5‡	4.9‡
SD	±1.7	±16.1	±27.5	±27.8	±14.0	±0.7	±0.7
Time to First Subjective Effect (min)							
Mean	8.0†	14.3	7.4	7.3	11.9	9.0	10.8
SD	±3.9	±8.7	±4.1	±2.3	±10.1	±1.4	±4.0

*Kruskal-Wallis ANOVA = 17.16, $P = 0.0000$, fast vs slow.
†Kruskal-Wallis ANOVA = 6.96, $P = 0.0084$, fast vs slow.
‡Kruskal-Wallis ANOVA = 11.80, df = 4, $P = 0.0189$, between dose differences.

was achieved by measuring the peak height ratio of fentanyl to carfentanil (internal standard). The lower limit of sensitivity was 0.2 ng/mL with the standard curve being linear between 2 and 20 ng/mL ($r^2 = 0.9996$). Higher concentrations were diluted until measured values fell within 0.2 and 20 ng/mL.

All data were analyzed for statistical significance using Kruskal–Wallis analysis of variance (ANOVA), 2-way ANOVA, and Spearman rank correlation. $P < 0.05$ was considered statistically significant.

Results

The 28 volunteers (23 male and 5 female) were all ASA I, 25–35 years old, and weighed 53–91 kg (Table 1). They received fentanyl lollipops containing 5 mg (N = 7), 4 mg (N = 3), 2 mg (N = 8), 1 mg (N = 2), and 0.5 mg (N = 8) of fentanyl citrate. Twenty of the 28 vounteers actively sucked on the lollipops [5 mg (N = 4), 4 mg (N = 2), 2 mg (N = 4), 1 mg (N = 2), and 0.5 mg (N = 8)] while 8 allowed the lollipops to dissolve passively [5 mg (N = 3), 4 mg (N = 1), 2 mg (N = 4)] (Table 1).

Consumption time was significantly less in subjects that actively sucked on lollipops (6.0 ± 1.7 min; mean ± SD) than in subjects who sucked slowly or not at all (43.6 ± 16.1 min, mean ± SD; $P = 0.0000$ Kruskal–Wallis ANOVA) and resulted in a more rapid onset of initial subjective changes [pleasant sleepy feeling; 8.0 ± 3.9 min (mean ± SD) vs. 14.3 ± 8.7 min; $P = 0.0084$ Kruskal–Wallis ANOVA] (Table 2).

Significant sedation (defined as a decrease from the baseline sedation score of one or more units) occurred more frequently after the highest doses of OTFC than after lower doses (Table 3), but was not related to the speed of lollipop consumption, Kruskal–Wallis ANOVA. Marked sedation (defined as a decrease in the baseline sedation score of two units) only occurred after OTFC dosages of 4 and 5 mg (Table 3), and was not influenced by speed of consumption, Kruskal–Wallis ANOVA. There was a high correlation between dose of OTFC and magnitude of sedation. Onset of sedation was variable (range 10 min to 4 hr) and not related to speed of lollipop consumption. Sedation did occur sooner after higher doses of OTFC (Table 3). Sedation was prolonged (>8 hr) in 5 of 7 volunteers receiving 5 mg

Table 3. Degrees of Sedation in 28 Volunteers Given Oral Transmucosal Fentanyl Citrate

	Fentanyl Citrate in Lollipop (mg)				
	5 N =7	4 N = 3	2 N = 8	1 N = 2	0.5 N = 8
Percent experiencing sedation*	100	100	88	50	38
Percent experiencing marked sedation†	[86	100]‡	[0	0	0]
Onset of sedation (min; mean ± SD)§	27.1 ± 16.0	20.0 ± 0.0	84.3 ± 88.1	60	36.67 ± 14.4

*Defined as a decrease from the baseline sedation score of one or more units; dose effect versus maximum sedation, $P = 0.0000$, df = 26, Spearman rank correlation = −0.82.

†Defined as a decrease from the baseline sedation score of two units.

‡$P = 0.0000$, Fisher exact test; doses = 5, 4 compared to doses 2, 1, 0.5.

§Defined as the time to decrease one or more activity units from baseline; dose effect versus onset of sedation, df = 18, Spearman rank correlation = −0.411.

Table 4. Changes in Pain Thresholds in 28 Volunteers Receiving Oral Transmucosal Fentanyl Citrate

	Fentanyl Citrate in Lollipop (mg)				
	5 N = 7	4 N = 3	2 N = 8	1 N = 2	0.5 N = 8
Percent Experiencing Analgesia	86.0	100.0	88.0	100.0	88.0
Baseline (mAmp) Pain Tolerated					
Mean	3.7	4.4	2.7	2.7	3.0
SD	±2.0	±4.4	±1.0	±0.7	±1.2
Onset of Analgesia (min)*					
Mean	25.0	16.7	27.9	20.0	26.4
SD	±16.1	±5.8	±9.06	±14.1	±18.9
Duration of Analgesia (min)					
Mean	[260.0	443.3]†	[99.3	47.5	67.9]
SD	[±175.6	±37.9]	[±83.5	±46.0	±41.8]
Maximum (mAmp) Pain Tolerated					
Mean	[9.6	21.6]‡	[4.7	3.9	4.4]
SD	[±6.2	±12.6]	[±3.5	±1.4	±2.1]

*Analgesia = 20% increase over baseline pain tolerated.

†Kruskal-Wallis ANOVA = 10.7, df = 1, $P = 0.0011$; doses = 5, 4 compared to doses = 2, 1, 0.5.

‡Kruskal-Wallis ANOVA = 7.88, df = 1, $P = 0.0050$; doses = 5, 4 compared to doses = 2, 1, 0.5.

of OTFC and all receiving 4 mg. Duration of sedation was variable with lower doses (30 min to >8 hr) and not related to dose or speed of consumption.

Onset of significant analgesia (defined as 20% or greater increase above baseline pain threshold) was variable (10–60 min) with all doses of OTFC and not related to speed of consumption. Some volunteers receiving high doses of OTFC (4 and 5 mg) developed marked analgesia (tolerated up to 32.2 mAmps, the maximal safe current) and would probably have tolerated higher currents which could have destroyed tissue. Peak analgesia (maximal tolerated electrical stimulation) was significantly greater and duration significantly longer after lollipops with 4 and 5 mg of fentanyl than with lower doses (Table 4). Analgesia also often lasted more than 8 hr with 4 and 5 mg of OTFC but was never present for more than 120 min after consumption of lollipops with 0.5 and 1 mg.

Respiratory rate was significantly lower after consumption of lollipops containing 4 and 5 mg of fentanyl than after lollipops containing 0.5, 1, and 2 mg (Table 5). Peak respiratory depression (minimal respiratory rate) was not influenced by speed of OTFC consumption. End-tidal CO_2 did not become elevated any sooner but did remain elevated longer after higher doses of OTFC (4 and 5 mg) than after lower doses (0.5, 1, and 2 mg). Speed of lollipop consumption did not affect the duration of respiratory depression. Peak end-tidal CO_2 values were similar irrespective of rate of suction but were higher after administration of 4 and 5 mg of OTFC than after 0.5, 1, and 2 mg.

Volunteers given 5, 4, and 2 mg doses of OTFC needed occasional reminders to "take a breath" because of decreases in oxygen saturation (Table 6). Time of onset of the hypoxic episodes was not corre-

Table 5. Respiratory Effects of 28 Volunteers Given Oral Transmucosal Fentanyl Citrate

	Fentanyl in Lollipop (mg)				
	5	4	2	1	0.5
	N = 7	N = 3	N = 8	N = 2	N = 8
Baseline Respiratory Rate (Breaths/min)					
Mean	13	13	14	13	12
SD	±3.5	±1.2	±0.7	±1.4	±1.6
Minimal Respiratory Rate					
Mean	5	6 *	8	12	10
SD	±2.0	±2.1	±2.1	±2.1	±0.5
$P_{ET}CO_2$ (Baseline) (mm Hg)					
Mean	37	37	41	37	39
SD	±5.5	±1.5	±4.9	±3.5	±3.0
Onset $P_{ET}CO_2 >$ Baseline + 3 mm Hg (min)					
Mean	27.9	20.0	26.9	50.0	46.4
SD	±18.7	±0.0	±8.9	±56.6	±35.9
Duration $P_{ET}CO_2 <$ Baseline + 3 mm Hg (min)					
Mean	349.3	440.0 ‡	228.1	130.0	56.4
SD	±153.7	±34.6	±74.4	±56.6	±44.0
Maximum $P_{ET}CO_2$ (mm Hg)					
Mean	54	52 †	51	43	43
SD	±7.9	±4.6	±5.8	±3.5	±3.7

*Kruskal-Wallis ANOVA = 15.13, df = 1, $P = 0.0001$; doses = 5, 4 compared to doses = 2, 1, 0.5.
†Kruskal-Wallis ANOVA = 5.35, df = 1, $P = 0.0208$; doses = 5, 4 compared to doses = 2, 1, 0.5.
‡Kruskal-Wallis ANOVA = 10.58, df = 1, $P = 0.0012$; doses = 5, 4 compared to doses = 2, 1, 0.5.

Table 6. Oxygen Desaturation after Oral Transmucosal Fentanyl Citrate in 28 Adult Volunteers

	Fentanyl in Lollipop (mg)				
	5	4	2	1	0.5
	N = 7	N = 3	N = 8	N = 2	N = 8
Volunteers with 1 or More Hypoxemic Episodes (%)	100	100	63	0	13
Time of Onset of First Hypoxic Episode (min)	N = 6	N = 3	N = 5	N = 0	N = 1
Mean	24.2	46.7	34.0	—	30
SD	±10.2	±37.9	±10.8	—	—
Respiratory Prompts (number)	157	23	16	0	0
Interval during Which Volunteers were Prompted to Breathe (min)	N = 6	N = 3	N = 3	N = 0	N = 0
Mean	150.8	16.7	35.0	—	—
SD	±171.0	±17.6	±48.2	—	—
Volunteers Requiring Naloxone (%)	14.3	0	0	0	0

lated to dose of OTFC or to speed of consumption. The incidence of hypoxic episodes, number of apneic prompts, and interval during which apneic prompting was necessary was also related to the dose of OTFC (Table 6). In spite of these problems only one subject needed naloxone at the end of the study. Only one of the volunteers receiving the two lower doses of OTFC experienced desaturation (Table 6); no volunteer receiving 0.5 and 1 mg required apneic prompting. Systolic arterial blood pressure and heart rate were not significantly altered in any volunteer at any time irrespective of speed of lollipop consumption or dose of fentanyl administered.

Only plasma samples from volunteers receiving 4 and 5 mg OTFC were available for analysis; test tubes containing the samples from volunteers receiving 0.5, 1, and 2 mg of OTFC were accidentally discarded. Although mean plasma concentrations of fentanyl were higher after consumption of 5 mg lollipops and rapid consumption (Figures 1 and 2), because of great variability, the differences were not quite statistically significant. Similarly, there was not a significant correlation (Spearman Rank correlation coefficient <0.05, $P > 0.2$) between plasma fentanyl concentrations and the measured analgesic and sedative effects. Plasma fentanyl levels reached values as great

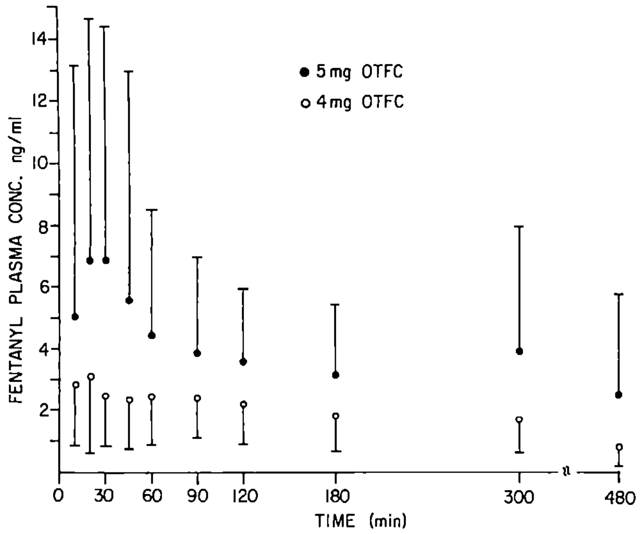


Figure 1. Plasma fentanyl concentrations (ng/mL) as a function of time (min) in 3 volunteers receiving OTFC with 4 mg of fentanyl and 7 receiving OTFC with 5 mg of fentanyl.

as 23 ng/mL early after consumption of 5 mg OTFC and ranged between 0.8 and 2.5 ng/mL after 8 hr (Figure 1).

Nausea (61%) and vomiting (11%) were limited to volunteers given 2, 4, and 5 mg doses of OTFC, were most often noted at the end of the study when the volunteers stood up, and were not related to speed of OTFC consumption (Table 7). Pruritus occurred in a high percentage (33%–87%) of volunteers irrespective of the dose of OTFC (Table 7). A number of volunteers (4 of the 18 volunteers receiving 5, 4, and 2 mg lollipops) complained of a headache at sometime during the study and three (1 receiving 5 mg and 2 having 4 mg OTFC) had transient difficulty with urination at the end of the study. No volunteer consuming 1 or 0.5 mg lollipops experienced headache or urinary retention and no subject became rigid or unconscious at any time during the study.

Discussion

The results of this study demonstrate that consumption of oral transmucosal fentanyl citrate (OTFC) results in rapid increases in plasma fentanyl levels with accompanying dose related sedation, analgesia, respiratory depression, and common opiate side effects (including pruritus, nausea, vomiting, and difficulty with micturition) but no changes in arterial blood pressure or pulse rate. The data indicate that low doses of OTFC (0.5 and 1 mg equivalent to 5–20 $\mu g \cdot kg^{-1}$ of fentanyl citrate) produce analgesia for short periods (1–2 hr) and some sedation (of variable duration) with minimal or no side effects and little respiratory depression. We believe low doses of OTFC deserve evaluation as premedication in patients; respiratory depression and a high incidence of side effects after higher doses of OTFC (4, 5, and 2 mg; >20 $\mu g \cdot kg^{-1}$) probably limit their usefulness for preoperative premedication.

Following the conclusion of this study, 2 volunteers who 30 days or more previously had rapidly consumed 5 mg of OTFC each swallowed an entire 5 mg lollipop (without the handle). Neither experienced noticeable sedation although both yawned and indicated they may have been a bit sleepy for about 15–20 min approximately 60–80 min after swallowing the candy. Unfortunately, instrumentation for measuring analgesia in these 2 subjects was not available, but end-tidal CO_2 determinations made 30, 60, 90, and 120 min after the candy was swallowed were the same as baseline values. These observations, when combined with the measurements made in our study, suggest (but do not confirm) that as the fentanyl containing candy dissolves in saliva and pharyngeal secretions, some must penetrate through the mucosa of the mouth, pharynx, and esophagus and enter the vasculature bathing these tissues. Venous drainage from the mouth, pharynx and esophagus reaches the right atrium and subsequently the systemic circulation without passage through the liver. In contrast, virtually all venous return from the stomach and small intestine passes through the liver via the portal circulation. The high hepatic clearance of fentanyl (10–20 $mL \cdot min^{-1}$) (3,10,11) proabably explains why volunteers swallowing 5 mg of the drug experienced little or no narcotic effects while buccal liquefaction of the same candy produced marked sedation, analgesia, and respiratory depression.

Volunteers given 4 and 5 mg of OTFC had profound analgesia and sedation and slept if undisturbed; none, however, lost consciousness or became rigid in spite of fentanyl plasma concentrations as high as 24 $ng \cdot mL^{-1}$. We believe these data are consistent with findings of Bailey and coworkers (12) who showed that young healthy patients often require enormous doses of fentanyl (and thus equally enormous plasma and brain concentrations) before consciousness is lost and that patients who do not become unconscious after fentanyl also do not become rigid.

Plasma concentrations obtained from volunteers receiving 5 mg of OTFC were higher than those from volunteers receiving 4 mg (Figure 1). However, because of a small N and the distribution of some of each group to active suction and others to passive suction (as well as the loss of plasma samples from

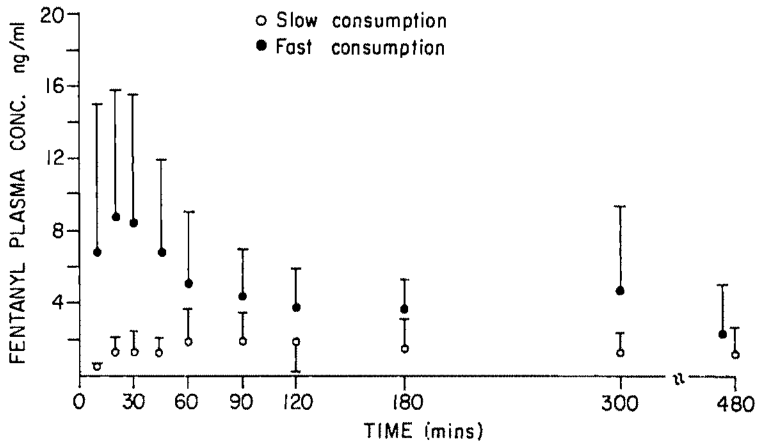


Figure 2. Plasma fentanyl concentrations (ng/mL) as a function of time (min) after fast (N = 6) and slow (N = 4) consumption of OTFC with 4 and 5 mg of fentanyl.

Table 7. Side Effects After Oral Transmucosal Fentanyl Citrate in 28 Adult Volunteers

	Fentanyl in Lollipop (mg)				
	5 N = 7	4 N = 3	2 N = 8	1 N = 2	0.5 N = 8
Nausea (%)	57	100	50	0	0
Emesis (%)	14	33	0	0	0
Pruritus (%)	71	33	87	50	40
Headache (%)	14	33	25	0	0
Urinary Retention (%)	14	66	0	0	0

volunteers receiving lower doses of OTFC), correlation between plasma levels of fentanyl and the measured sedative and analgesic effects was poor.

Although respiratory depression after 0.5 and 1 mg of OTFC was minimal, the large range of responses in our volunteers suggests that even after these doses continuous respiratory monitoring is indicated. Early clinical experiences demonstrate that OTFC in doses as high as 15–20 $\mu g \cdot kg^{-1}$ does not result in oxygen saturations <90% (as measured by digital pulse oximetry) but doses >20 $\mu g \cdot kg^{-1}$ do cause occasional desaturation (13,14). The ultimate value of OTFC as premedication in children will depend on finding a dose range which results in adequate sedation without concomitant respiratory depression. Additional clinical investigations should also probably evaluate OTFC as an alternate route for the delivery of analgesic doses of fentanyl.

References

1. Henderson JM, Brosdky DA, Fisher DM, Brett CM, Hertzka RE. Preinduction of anesthesia in pediatric patients with nasally-administered sufentanil. Anesthesiology 1988;68:671–5.
2. Stanley TH. New routes of administration and new delivery systems of anesthetics. Anesthesiology 1988;68:665–8.
3. McClain DA, Hug CC. Intravenous fentanyl kinetics. Clin Pharmacol Ther 1980;28:106–14.
4. Herz A, Teschermacher HJ. Activities and sites of antinociceptive action of morphine-like analgesics and kinetics of distribution following intravenous, intracerebral and intraventricular application. In: Harper NJ, Simmonds AB, eds. Advances in drug research, vol. 6. New York: Academic Press, 1971: 79–119.
5. Leysen JE, Laduron PM. Receptor binding properties in vitro and in vivo of some long acting opiates. Arch Int Pharmacodyn Ther 1978;232:343–6.
6. Parry WL, Smith GM, Denton JE. An electrical-shock method of inducing pain responsive to morphine in man. Anesth Analg 1972;51:573–8.
7. Tursky B, Watson PD, O'Connell DN. A concentric shock electrode for pain stimulation. Psychophysiology 1965;1:296–8.
8. Bailey PL, Williard KF, Pace NL, Stanley TH. Transcutaneous cranial electrical stimulation, experimental pain and plasma B-endorphine in man. Pain 1984:Suppl 2:S66.
9. Bailey PL, Port JD, McJames S, et al. Is fentanyl an anesthetic in the dog? Anesth Analg 1987;66:542–8.
10. Hug CC Jr. Pharmacokinetics of new synthetic narcotic analgesics. In: Estafanous FG, ed. Opioids in anesthesia. Boston: Butterworth, 1984:50–60.
11. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 1982;54:871–7.
12. Bailey PL, Wilbrink J, Zwanikken P, Pace NL, Stanley TH. Anesthetic induction with fentanyl. Anesth Analg 1985;64:48–53.
13. Streisand JB, Stanley TH, Hague B, van Vreeswijk H, Ho GH, Pace NL. Oral transmucosal fentanyl citrate (lollipop) premedication in children. Anesth Analg (In press).
14. Nelson PS, Streisand JB, Mulder S, Pace N, Stanley TH. Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam and atropine for premedication in children. Anesthesiology 1989;70:616–21.

ANESTH ANALG
1989;69:28–34

Oral Transmucosal Fentanyl Citrate Premedication in Children

James B. Streisand, MD, Theodore H. Stanley, MD, Brian Hague, BS,
Hans van Vreeswijk, drs, Gwan H. Ho, drs, and Nathan L. Pace, MD

STREISAND JB, STANLEY TH, HAGUE B, VAN VREESWIJK H, HO GH, PACE NL. Oral transmucosal fentanyl citrate premedication in children. Anesth Analg 1989;69:28–34.

The authors evaluated the safety and efficacy of four doses of oral transmucosal fentanyl citrate (OTFC) as a premedicant in 44 children about to undergo elective operations. The patients received 5–10, 10–15, 15–20, or 20–25 $\mu g \cdot kg^{-1}$ of OTFC in the holding area and had activity (sedation) scores, vital signs (including systolic and diastolic arterial blood pressures, heart, and respiratory rates), and pulse oximetry determined oxygen saturation measured before and at 15-min intervals after premedication until they were taken to the operating room. Cooperation during anesthetic induction, and quality and speed of recovery room emergence were measured and side effects noted. OTFC was readily accepted and provided significant (dose dependent) reductions in preoperative activity starting after 30 min. Onset of sedation was related to dose of OTFC but time to peak effect was not. Vital signs remained unchanged preoperatively in all groups but patients receiving 20–25 $\mu g \cdot kg^{-1}$ had oxygen saturations that were significantly lower than patients in the other groups 30 min after beginning OTFC consumption. Three of the 12 patients receiving the highest dose of OTFC experienced transient oxygen saturation <90% which, however, was easily treated by commands to take a breath. Anesthetic inductions were rated good or excellent in 80% of the patients and recovery times were similar irrespective of the OTFC dose. OTFC caused dose–independent preoperative pruritus in 90% or more of patients and pruritus (33%–70%), nausea (30%–58%), and vomiting (50%–83%) postoperatively. The data suggest that 15–20 $\mu g \cdot kg^{-1}$ is the optimal dose range of OTFC in healthy children for optimizing onset (18.0 ± 10.3 min) and magnitude (92% calm, sedated or asleep) of preoperative sedation and minimizing preoperative respiratory side effects (lowest respiratory rate = 15.9 ± 4.1 breaths/min and lowest oxygen saturation 95.3 ± 1.6%). OTFC should be compared to other premedicants using more traditional routes of delivery to determine if its benefits outweigh associated side effects.

Key Words: ANESTHESIA, PEDIATRIC—premedication. PREMEDICATION—oral transmucosal. ANALGESICS—fentanyl.

Previous experience in adult volunteers demonstrated that fentanyl incorporated into a candy matrix (lollipop) can be absorbed through the oral mucosa to produce sedation, analgesia, and respiratory depression (1). Although the initial study suggested oral transmucosal fentanyl citrate (OTFC) might be a novel way of delivering premedication to children, ideal dose ranges were unknown and clinical experience in the pediatric population did not exist. The objectives of this study were to evaluate the acceptability of OTFC premedication and to determine a reasonable dose range in children about to undergo elective in–patient and out–patient operations.

Methods

Approval was received from the Food and Drug Administration and the University of Utah Human Institutional Review Board, and written informed consent was obtained from the parents of 47 ASA Class I–II children aged 2 to 13 yr scheduled for a variety of elective ophthalmologic, otolaryngologic (ENT), urologic, and orthopedic operations. The children were randomly assigned to one of four groups according to the dose of fentanyl citrate they were to receive in the lollipop: group I, 5–10 $\mu g \cdot kg^{-1}$; group II, 10–15 $\mu g \cdot kg^{-1}$; group III, 15–20 $\mu g \cdot kg^{-1}$; and group IV, 20–25 $\mu g \cdot kg^{-1}$. No placebo was used and

---

Received from the Department of Anesthesiology, The University of Utah School of Medicine, Salt Lake City, Utah. Accepted for publication February 1, 1989.

Supported in Part by Stanley Research Foundation.

Address correspondence to Dr. Streisand, Department of Anesthesiology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132.

©1989 by the International Anesthesia Research Society

no attempt was made to blind the study because of the limited experience with OTFC in adults and no previous experience in children.

Lollipops were made by heating a flavored candy base and dissolving the appropriate, measured amount of fentanyl citrate into the mixture. The liquid candy-fentanyl mixture was poured into molds, a stick added and the lollipops allowed to harden. Lollipops were made containing 100, 200, 300, 400, 500, 700, and 1000 μg of fentanyl citrate. All lollipops were the same size (1.6 cc) irrespective of the dose of fentanyl they contained. If either of two doses of OTFC (e.g., 100 or 200 μg lollipop) was appropriate for the group to which the child was allocated, the lower dose was chosen.

Approximately 1 hr before the scheduled beginning of the operation each child (accompanied by his or her parents) was brought to the preoperative holding area adjacent to the operating room. After examination of the patient's oral mucosa, baseline systolic (SBP) and diastolic (DBP) arterial blood pressures, heart rate (HR), respiratory rate (RR), and oxygen saturation (O_2 Sat) were measured by: a standard manual pediatric blood pressure cuff, radial arterial palpation, observation of the chest wall, and use of a Criticare Systems Model 501 pulse oximeter, respectively. The patients were then given a lollipop with the appropriate dose of OTFC and were asked to rapidly suck it without biting or chewing it. The time required for complete consumption of the candy was recorded.

Oxygen saturation was continuously measured and HR, SBP, DBP, and RR remeasured every 15 min throughout the preanesthetic evaluation period until the children were taken to the operating room. Activity (sedation) scores (Table 1) evaluating the effectiveness of the premedication were also determined at baseline (prior to premedication administration), every 15 min thereafter, and immediately before the children were taken to the operating room. Time between start of lollipop consumption and first effect, defined as the appearance of nasal pruritus or a decrease in the activity score of one or more, was recorded for each patient. Prior to departure to the operating room, the patient's oral mucosa was reexamined. Each child's response to the operating room and ability to cooperate with the anesthesiologist just prior to anesthetic induction was evaluated using a scoring scale (Table 1).

Anesthesia was induced with halothane (0.25%–4.0%) and N_2O (60%) in oxygen via a face mask. Ventilation was at first spontaneous, then assisted, and finally controlled as the patient lost consciousness. After loss of consciousness an intravenous infusion of 5% dextrose in 0.25% normal saline or lactated Ringer's solution was started in a hand or arm vein. The trachea was intubated without the use of a muscle relaxant unless laryngeal exposure was difficult or anatomic considerations suggested that paralysis would significantly facilitate endotracheal intubation. In these circumstances succinylcholine (1.0–1.5 mg·kg^{-1} IV) was used for relaxation. Anesthesia was maintained with halothane (0.1%–2.5%) or isoflurane (0.2%–2.0%) and N_2O (60%) in oxygen in concentrations that kept SBP within 20% of preoperative values. No narcotics, anti–emetics or intravenous anesthetics were used; muscle relaxants were used after endotracheal intubation if clinically indicated. Generally, controlled ventilation was maintained until 10–20 min before the end of the operation when halothane or isoflurane concentrations were decreased or discontinued and spontaneous ventilation resumed. Endotracheal tubes were removed when patients first responded to them, when the respiratory rate was >12 breaths/min, and when the tidal volume was considered to be clinically adequate.

Table 1. Scoring Schedules for Evaluation of Preoperative Activity (Sedation), the Level of Cooperation Prior to Induction of General Anesthesia, and Reactivity During Emergence From General Anesthesia

Preoperative activity
1 = Asleep; not readily arousable
2 = Asleep; responds slowly to verbal commands
3 = Drowsy; readily responds to verbal commands
4 = Awake; calm and quiet
5 = Awake and active

Preinduction cooperation
1 = Excellent (none of the conditions listed below as A, B or C)
2 = Good (1 of conditions A, B or C)
3 = Fair (2 of conditions)
4 = Poor (all 3 of conditions A, B and C)
  A. Crying
  B. Need for restraint
  C. Avoidance

Emergence
1 = Excellent (quiet)
2 = Good (occasional crying)
3 = Fair (crying, but able to be quieted)
4 = Poor (thrashing, unable to be quieted)

Emergence from anesthesia was evaluated in the recovery room every 30 min using an emergence scoring scale (Table 1). Times to awakening (as measured from discontinuation of all inhalation anesthetics until spontaneous eye opening first occurred) and first response to verbal commands (as measured from termination of all inhalation anesthetics until eye opening first occurred upon command) were evalu-

Table 2. Demographic Data in 44 Children Premedicated with 1 of 4 Doses of Oral Transmucosal Fentanyl Citrate, OTFC (Mean ± SEM)

Group	I	II	III	IV
OTFC Dose ($\mu g \cdot kg^{-1}$)	5–10	10–15	15–20	20–25
Patients (n)	10	10	12	12
Gender M/F	7/3	6/4	7/5	8/4
Age (yr)	6.9 ± 0.9	7.1 ± 1.2	8.0 ± 0.9	6.5 ± 0.9
Weight (kg)	23.9 ± 3.6	24.7 ± 3.6	26.0 ± 2.9	23.3 ± 2.9
Duration of Anesthesia (min)	119 ± 36	126 ± 19	81 ± 12	158 ± 20
Lollipop Consumption Time (min)	18.4 ± 12.3	14.5 ± 6.3	13.4 ± 7.5	15.4 ± 9.6

ated every 5 min in the recovery room and recorded. Intravenous narcotics (morphine 0.5–1.0 mg or meperidine 5–10 mg) were administered by the recovery room nurses (who were unaware of the premedication used) for control of moderate or severe postoperative pain (as determined by a physician uninvolved with the study). Patients were discharged from the recovery room when they achieved a score of 10 using the Aldrete postanesthetic recovery score (2). Recovery time, defined as time from arrival in the recovery room to fulfillment of discharge criteria, was recorded. The incidences and times of occurrence of pruritus and nausea (as volunteered by the patient) and vomiting were recorded in the preoperative holding area, operating room, and recovery room.

Statistical Methods

Data were analyzed for statistical significance using a two-way analysis of variance for age and weight; a chi-square analysis for gender, and a Mantel–Haenszel chi-square analysis for ASA class distribution. The time it took for consumption of the OTFC, the duration of anesthesia, and recovery were compared across groups by one-way analysis of variance, as were comparisons of the effect of dose on SBP, DBP, HR, RR, and O_2 saturation. Statistically significant differences between vital sign values at baseline and during peak sedative effect were evaluated using a repeated measures two-way analysis of variance (ANOVA). The Kruskal–Wallis one-way ANOVA was used to examine the time of the lowest vital signs and O_2 saturation. ANOVA for linear trends was used to examine dose effect for the peak respiratory rate change. Comparisons of O_2 saturation between groups were performed with the Duncan's multiple range test; chi square and chi square for linear trends were used to compare the effect of dose on the appearance of low oxygen saturation (oxygen saturation <90%).

The effect of dose on the activity (sedation) score was compared by Mantel–Haenszel chi-square analysis; the effect of dose on the time to peak sedation was compared by one-way ANOVA. The change in activity over time was examined by a Wilcoxon test; a Bonferroni adjustment was made to the *P* values. Onset of sedation was evaluated via a Brown Forsythe one-way ANOVA and Duncan's multiple range test, and ANOVA for linear trends was used to examine dose effect on onset time for sedation. The Mantel–Haenszel chi-square analysis was used to evaluate the cooperation of the patient prior to anesthetic induction and the effect of dose on the incidence of side effects.

The majority of the analyses were performed with the BMDP and STAT 80 statistical package (3). $P < 0.05$ was considered statistically significant.

Results

Although 47 children were entered in the study, data for only 44 were evaluated. The remaining 3 were eliminated from consideration because they refused to take the lollipop (2) or were called to the operating room before they had sufficient time to finish it (1). Of the 44 children evaluated, 10 were in each of groups I and II, and 12 in each of groups III and IV. The four groups were similar with respect to gender distribution, the type of operation scheduled, ASA physical status distribution, age, weight, baseline vital signs, and duration of anesthesia (Table 2). The duration of administration (mean lollipop consumption times) ranged from 2 to 50 min but averaged about 15 min and were similar in the four groups (Table 2). Oral mucosal observations (before and after premedication) were normal in each child.

All 44 children had preoperative evaluations for at least 15 min and some for as long as 90 min after baseline. Numbers of children evaluated in the four groups decreased with each additional 15-min interval after 15 min as increasing numbers of patients were called to the operating room. Evaluations at 30, 45, 60, 75, and 90 min after baseline included 42, 22, 11, 7, and 2 patients, respectively. Statistical analysis

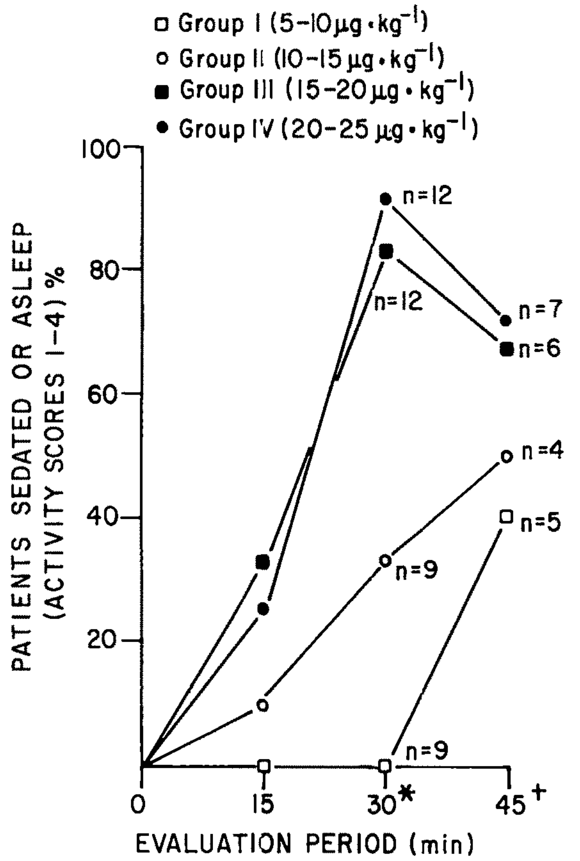


Figure 1. Percent of patients sedated or asleep (activity scores 1–4) as a function of time in children premedicated with oral transmucosal fentanyl citrate (OTFC) in the doses indicated. $^*P = 0.0001$, $+P = 0.0002$, when all patients considered as one group are compared to baseline, Wilcoxon test.

after 45 min was done but is not presented because of low N values.

Analysis of change from baseline for activity showed significant increases in sedation at 30 and 45 min, immediately prior to leaving the holding area, and at peak sedative effect (Figure 1). In addition, there were significant positive relationships between increasing dose and increasing sedation 30 min after beginning consumption, prior to leaving the holding area, and at peak effect (Table 3). Onset of sedation occurred significantly sooner with higher doses of OTFC, but time to peak effect did not.

The four groups had similar arterial blood pressures and heart and respiratory rates at baseline and at all evaluation periods in the preoperative holding area. Similarly, there were no differences between the four groups in the lowest systolic and diastolic arterial blood pressures and heart rates recorded or the time of these lowest recordings (Table 4). There were no consistent relationships between the lowest hemodynamic values and any other variable measured during the study. None of the lowest values recorded was considered of clinical importance. There was a significant relationship between increasing dose of OTFC and the lowest respiratory rate recorded (Table 4), although there was no relationship between dose and the time of lowest respiratory rate. Oxygen saturation (of all patients considered as one group) was significantly lower at the time of peak oxygen saturation depression (two-way ANOVA; $F_{1,37} = 56.03$) than at baseline. Patients in group IV had oxygen saturations which were significantly lower than those in groups I, II, and III 30 min after beginning OTFC consumption (Figure 2) and at the time of peak depression of oxygen saturation (Table 4). Three children in group IV had transient decreases in oxygen saturation to ≤89% in the holding area (range 84%–89%). This incidence (25%) was significantly ($\chi^2 = 8.33$) greater than in the other three groups (0%); in all instances oxygen saturations returned to normal with commands to breathe.

Thirty–three of the 44 children had evaluations immediately prior to anesthetic induction rated as excellent (Figure 3), but there were no statistical differences between the groups. Emergence scores of the four groups in the recovery room were not statistically different at anytime. There were no significant differences in the times to awakening, first response to verbal command, and fulfillment of criteria for discharge from the recovery room in the four groups (Table 5).

In the preoperative holding area nausea occurred in two patients in group III and one patient in group IV vomited. In contrast, mild facial pruritus occurred in 90% or more of patients in all groups and coincided with the onset of sedation (Table 6). The incidence of these side effects in the holding area were similar in the four groups. No patient had nausea, vomiting or pruritus in the operating room. Pruritus occurred postoperatively in all groups but was inversely related to dose ($MH\chi^2 = 4.579$, $P = 0.0324$, Mantel–Haenszel chi-square test). The incidences of postoperative nausea (30%–58%) and vomiting (50%–83%) were not significantly different amongst the four groups. There was no relationship between the incidence of preoperative or postoperative side effects and their time of lollipop consumption or the duration of stay of the patient in the holding area. No patient became rigid at any time during the study. Naloxone was given to two patients (one each in groups III and IV) for a postoperative respiratory rate <12 breaths·min^{-1} and two other patients in group IV required occasional encouragement to maintain respiratory rates >12 breaths·min^{-1} for a short time (5–10 min) in the recovery room. One patient (group I) developed hiccoughs, one (group IV) had laryngo-

Table 3. Activity (Sedation) in 44 Children Premedicated with 1 of 4 Doses of Oral Transmucosal Fentanyl Citrate

Group Dose of Fentanyl ($\mu g \cdot kg^{-1}$)	I 5–10	II 10–15	III 15–20	IV 20–25
*Patients Calm, Sedated or Asleep (Activity Scores 1–4) Immediately Prior to Leaving the Holding Area (%)	30	50	80	92
†Patients Calm, Sedated or Asleep (Activity Scores 1–4) at Peak Sedative Effect (%)	30	50	92	92
**Time to Onset of Sedation (min; mean ± SD)	31.7 ± 20.7	18.9 ± 5.9	18.0 ± 10.3	14.1 ± 5.2
Time to Peak Sedation (min; mean ± SD)	65.0 ± 22.9	39.0 ± 22.3	34.1 ± 17.9	36.4 ± 10.9

*$MHX^2 = 7.29$, $P = 0.0069$; increasing sedation with increasing dose.
†$MHX^2 = 11.62$, $P = 0.0007$, increasing sedation with increasing dose.
**Dose vs time to onset significantly related, ANOVA for linear regression $F_{1,42} = 11.11$, $P = 0.0019$.

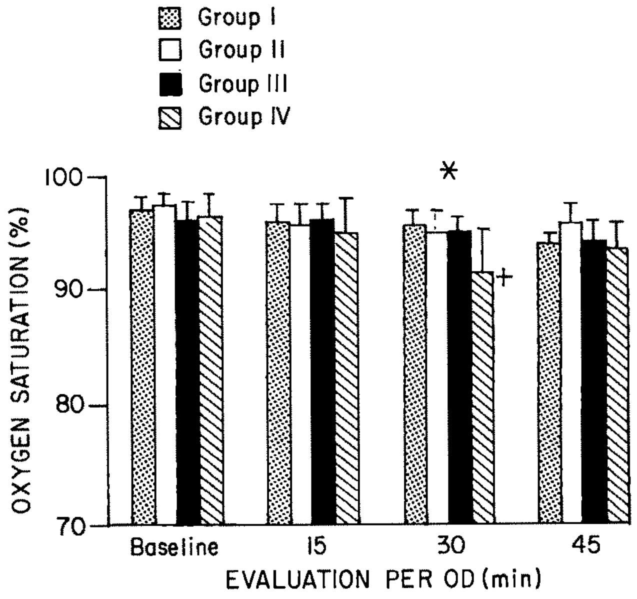
Table 4. Lowest Arterial Blood Pressures, Heart Rates and Respiratory Rates in 44 Children Premedicated with 1 of 4 Doses of Oral Transmucosal Fentanyl Citrate (Mean ± SD)

Group Dose of fentanyl ($\mu g \cdot kg^{-1}$)	I 5–10	II 10–15	III 15–20	IV 20–25
Lowest Systolic Blood Pressure (mm Hg)	98.9 ± 15.0	93.4 ± 11.3	91.4 ± 7.3	94.4 ± 13.3
Lowest Diastolic Blood Pressure (mm Hg)	60.0 ± 10.4	59.1 ± 9.4	59.4 ± 8.3	60.9 ± 6.6
Lowest Heart Rate ($Beats \cdot min^{-1}$)	91.8 ± 17.6	94.3 ± 20.8	88.2 ± 19.2	95.3 ± 13.2
Lowest Respiratory Rate* ($Breaths \cdot min^{-1}$)	18.3 ± 3.3	16.4 ± 4.9	15.9 ± 4.1	13.8 ± 2.8
Lowest Oxygen Saturation (%)	95.6 ± 2.0	95.3 ± 2.3	95.3 ± 1.6	91.7 ± 4.3†

*ANOVA for linear trends, $F_{3,39} = 7.26$, $P = 0.0100$; lowest respiratory rate linearly related to dose.
†Group IV is significantly lower than groups I, II and III (Duncan's multiple range test at a 95% confidence level).

spasm, and one (group II) had a mild preoperative upper respiratory infection and was febrile (39°C) postoperatively. The latter patient was admitted for overnight intravenous penicillin therapy and was discharged afebrile the following day. One patient (group II) developed a short run of premature ventricular contractions which abated without treatment. No other side effects were noted.

Figure 2. Mean (±SD) arterial oxygen saturation measured by pulse oximetry in children premedicated with oral transmucosal fentanyl citrate (OTFC). *$P < 0.01$; difference among groups. +Group IV significantly lower than groups I. II and III (Duncan's multiple range; 95% confidence level).



Discussion

In this study oral transmucosal fentanyl citrate (OTFC) was readily accepted by 45 of 47 children and provided significant increases in sedation and good or excellent conditions for induction of anesthesia in 35 of the 44 evaluable patients. We believe the results demonstrate that OTFC is effective and, in doses <20 $\mu g \cdot kg^{-1}$, safe in children when used as a premedicant prior to induction of anesthesia. Onset of sedation is faster and peak sedative effect is greater with higher doses but changes in hemodynamics are minimal and not related to dose. As expected, OTFC produced dose related decreases in respiratory rate. Children

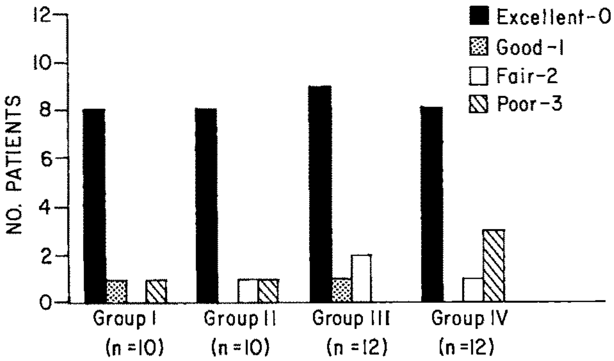


Figure 3. Children's poise and level of cooperation with the anesthesiologist just prior to anesthetic induction.

receiving the highest doses of fentanyl (group IV; 20–25 $\mu g \cdot kg^{-1}$) had significantly lower pulse oximeter measured oxygen saturations than patients receiving lower doses after 30 min. Twenty-five percent of group IV had transient arterial oxygen desaturation prior to induction of anesthesia. The other principal side effects associated with OTFC premedication were pruritus preoperatively and pruritus, nausea and vomiting postoperatively. The data suggest that 15–20 $\mu g \cdot kg^{-1}$ is the optimal dose range of OTFC premedication in healthy children in terms of optimizing preoperative sedation and minimizing preoperative respiratory side effects.

Our experience to date, and the work of Leiman and coworkers (4) and Nelson et al. (5) confirm that clinically significant respiratory depression is rare after OTFC given in doses of 15–20 $\mu g \cdot kg^{-1}$ or lower. Only one of 72 children receiving these doses of OTFC in the three studies developed arterial oxygen desaturation and that was transient. Nonetheless, the potential for respiratory depression and perhaps the occasional need for naloxone postoperatively after OTFC probably exists irrespective of the dose employed; this mandates that oxygen saturation be monitored during and possibly after (in the recovery room) its use. Oxygen desaturation occurring in the three patients in group IV in this study was easily managed by encouraging the patients to breathe.

All doses of OTFC were associated with a high incidence of facial pruritus preoperatively (90%–100%) and postoperatively (33%–70%). Similar incidences have been found in other studies in which OTFC was used for premedication in children (4,5). Pruritus was a valuable sign in this study because it heralded the onset of sedation; pruritus was not disturbing to the children or their parents. The incidences of postoperative nausea (30%–58%) and vomiting (50%–83%) were high in this study and probably were at least partially due to fentanyl. On the other hand, 30 of the 44 patients had strabismus and related ophthalmologic operations or ENT surgery and most were outpatients. Similar incidences of postoperative nausea and vomiting have been reported by others in outpatient children having eye and ear operations and especially after premedication with a narcotic analgesic and omission of anti–emetic prophylaxis (6–11).

The influence of OTFC on the volume and pH of gastric contents and preoperative nausea and vomiting are potential concerns. Gastric volume and pH evaluations were not made in this study but have been done in a recent investigation by Leiman and coworkers (4). These investigators found that compared to children receiving no premedication or a placebo lollipop, with OTFC changes in gastric pH and volume were statistically insignificant. Nonetheless, whether a rapid sequence induction with airway protection is indicated rather than a slow inhalation induction without additional attention to the airway is a potential issue in a child that complains of nausea or vomits preoperatively.

This study might be criticized for not employing an alternative premedication and/or a placebo control for comparison as well as for not using a double-blind approach for administration of the premedicants and evaluation of the patients. The study was performed open and without comparison groups because there was no previous clinical experience with OTFC in children or adults. In addition, even though fentanyl is a well known drug, this study was considered a phase I trial of a new delivery system. Phase I trials, by definition, do not employ comparison groups or double–blind approaches in the interest of patient safety. In spite of being an open study, we believe that the data are valuable because the patients were unaware of their group allocations and the scoring schedules used reasonably objective end points. Furthermore, most side effects (respiratory depression, pruritus, and vomiting) were obviously present or absent.

This study may also be criticized for not providing evaluations of sedation, vital signs, and oxygen saturation in all patients 30, 40, 60 min, and longer after beginning consumption of OTFC. Evaluations at 30 min and later were accomplished in less than 44 patients because our patients were being progressively called to the operating room and we were committed to avoidance of delay in our operating room schedule. Because some of our patients were late in arriving in the preoperative holding area and, therefore, were late having their baseline data recorded and premedication administered, we had to

Table 5. Recovery Room Data in 44 Children Given Oral Transmucosal Fentanyl Citrate (OTFC) for Premedication (Mean ± SD)

Group	I	II	III	IV
Dose Range of OTFC ($\mu g \cdot kg^{-1}$)	5–10	10–15	15–20	20–25
	Time from Last Anesthetic Agent off (Min) to:			
Awakening (Spontaneous Eye Opening; min)	46.4 ± 33.6	40.4 ± 21.2	33.7 ± 22.0	37.9 ± 20.6
First Response to Verbal Command (min)	48.2 ± 24.4	46.6 ± 24.1	38.3 ± 21.6	43.5 ± 17.0
Recovery Room Discharge (min)	79.4 ± 49.7	70.0 ± 21.7	75.8 ± 65.7	85.6 ± 36.7

Table 6. Incidence of Side Effects in 44 Children Given Oral Transmucosal Fentanyl Citrate (OTFC) Premedication (%)

Group	I	II	III	IV
Dose Range of OTFC ($\mu g \cdot kg^{-1}$)	5–10	10–15	15–20	20–25
N	10	10	12	12
Preoperative				
Pruritus	90	90	92	100
Nausea	0	0	17	0
Vomiting	0	0	0	8
Operating Room				
Pruritus	0	0	0	0
Nausea	0	0	0	0
Vomiting	0	0	0	0
Recovery Room				
Pruritus	70	70	33	33
Nausea	50	30	42	58
Vomiting	80	80	50	83

allow them to leave the holding area sooner than expected.

The ease of patient acceptance, rapid onset of sedation, high incidence of good or excellent conditions for induction of anesthesia, and apparent lack of prolonged recovery after OTFC suggest it may have value as a premedicant in healthy children. Although premedication may not be appropriate for every child, because of the associated side effects and need for oxygen saturation monitoring, OTFC may play a role in the perioperative management of the nervous, frightened, and psychologically unprepared child. We believe these findings indicate that OTFC should be compared to other premedicants using more traditional routes of administration in children to determine if the benefits of this form of premedication outweigh the associated side effects of pruritus, nausea, vomiting, and infrequent postoperative respiratory depression.

References

1. Stanley TH, Hague B, Mock DL, Streisand JB, Bubbers S, Dzelzkalns RR, Bailey PL, Pace NL, Earrus B, East KA, Stanley TO. Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers. Anesth Analg (in press).
2. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg 1970;49:924–34.
3. BMDP Statistical Software, Department of Biomathematics, UCLA. Berkeley, California: University of California Press, 1981.
4. Leiman BC, Walford A, Rawal N, Katz J, Marcus M, van Nieuwenhuyzen M, Cronau L, Stanley TH. The effects of oral transmucosal fentanyl citrate premedication on gastric volume and acidity in children (abstract). Anesthesiology (in press).
5. Nelson PS, Streisand JB, Mulder SM, Pace NL, Stanley TH. Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam and atropine for premedication in children. Anesthesiology 1989;70:616–21.
6. Palazzo MGA, Strunin L. Anaesthesia and emesis. I. Etiology. Can J Anaesth 1987;31:178–87.
7. Abramowitz MD, Oh TH, Epstein BS, Ruttsman UE, Friendly DS. The antiemetic effect of droperidol following outpatient strabismus surgery in children. Anesthesiology 1987;59:579–83.
8. Wilton NCT, Burns JMB. Delayed vomiting after papaveretum in paediatric outpatient surgery. Can Anesth Soc J 1986;33:741–3.
9. Burtles R, Peckett BW. Postoperative vomiting. Br J Anaesth 1957;29:114–23.
10. Smith BL, Manford MLM. Postoperative vomiting after paediatric adenotonsillectomy. Br J Anaesth 1974;46:373–8.
11. Rowley MP, Brown TCK. Postoperative vomiting in children. Anaesth Intens Care 1982;10:309–13.

Hemodynamic and Cardiodynamic Effects of Propofol and Etomidate: Negative Inotropic Properties of Propofol

Thomas Brüssel, MD, Josef L. Theissen, MD, Gisli Vigfusson, MD,
P. Paul Lunkenheimer, MD, Hugo Van Aken, MD, and Peter Lawin, MD

BRÜSSEL T, THEISSEN JL, VIGFUSSON G, LUNKENHEIMER PP, VAN AKEN H, LAWIN P. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. Anesth Analg 1989;69:35–40.

The hemodynamic effects of an induction dose of propofol, 2.5 mg/kg, or etomidate, 0.3 mg/kg, were studied in eight dogs. In addition, cardiodynamic changes were measured using a left ventricular catheter and needle force probes. Propofol was associated with significant decreases in systolic (19.9%) and diastolic (25.3%) arterial pressures associated with a 17.3% decrease in cardiac output (CO) and a 11.6% reduction in systemic vascular resistance (SVR) without change in pulmonary capillary wedge pressure (PCWP). These changes were most pronounced 1 min after the injection of propofol. At 5 and 10 min after the administration of propofol, heart rate (HR) decreased significantly. Minimal changes in hemodynamics were observed with etomidate. Propofol lowered systolic left ventricular pressure (LVPsys) by 17.6%. Signals generated by the force probes in the left ventricular myocardium showed a significant reduction (16.3%) in left ventricular force (LVF) and a decrease in early systolic rates of increase in force (dF/dt max) by 23.5% associated with propofol. In the presence of an unchanged preload, an unchanged HR, and a decreased SVR, the reduction in CO suggests that propofol has a negative inotropic effect. This negative inotropic effect was confirmed by a reduction in LVF and dF/dt max.

Key Words: ANESTHETICS, INTRAVENOUS—propofol, etomidate.

Propofol (2,6 diisopropylphenol) is an intravenous anesthetic that is currently undergoing clinical trials in the United States. Propofol, as 1% w/v aqueous solution in 10% w/v soya bean oil, 1.2% egg phosphatide, and 2.25% w/v glycerol, has pharmacological properties similar to the earlier formulation with Cremophor EL (1–3), but due to a loss of potency, the recommended induction dose is slightly greater (1). The induction of anesthesia with propofol is often associated with a marked decrease in systemic arterial pressure in humans (1–11). Whether this effect is the result of a decrease in preload, a decrease in afterload, a negative inotropic property of the drug, or the combination of all the above cannot be ascertained from the literature as the results of different studies are conflicting. The aim of this study was to determine the role, if any, of the negative inotropic effect of propofol in causing arterial hypotension. The responses to propofol were compared to those produced by etomidate. Both drugs were used in doses recommended for the induction of anesthesia in humans. The study was approved by the University of Münster, Medical Faculty Animal Investigation Committee.

Methods

Eight mongrel dogs of both sexes weighing 38.1 ± 8.5 kg were studied. The animals were premedicated with ketamine, 12 mg/kg IM. Anesthesia was then induced with ketamine, 1 mg/kg IV, and fentanyl, 25 μg/kg IV. After tracheal intubation the animals were mechanically ventilated with 67% nitrous oxide in oxygen. In addition, anesthesia was maintained by a continuous infusion of ketamine, 9 mg kg^{-1} hr^{-1}, and fentanyl, 3 μg kg^{-1} hr^{-1}, throughout the entire experiment. Carbon dioxide tension was kept between 38 and 42 mm Hg as assessed by continuous measurement of end-tidal carbon dioxide concentration and the repetitive analysis of arterial blood gas

---

Received from the Klinik und Poliklinik für Anaesthesiologie und operative Intensivmedizin der Westfälischen Wilhelms-Universität, Albert-Schweitzer-Strasse 33, Münster, West Germany. Accepted for publication January 16, 1989.

Supported by ICI-Pharma.

Address correspondence, after August 15, 1989, to Dr. Brüssel, Klinik und Poliklinik für Anaesthesiologie und operative Intensivmedizin der Westfälischen Wilhelms-Universität, Albert-Schweitzer-Strasse 33, 4400 Münster, West Germany. Before August 15, address correspondence to Dr. Brüssel c/o Bart Chernow, MD, Department of Anesthesia, Gray 3A, Massachusetts General Hospital, Fruit Street, Boston, MA 02114.

©1989 by the International Anesthesia Research Society

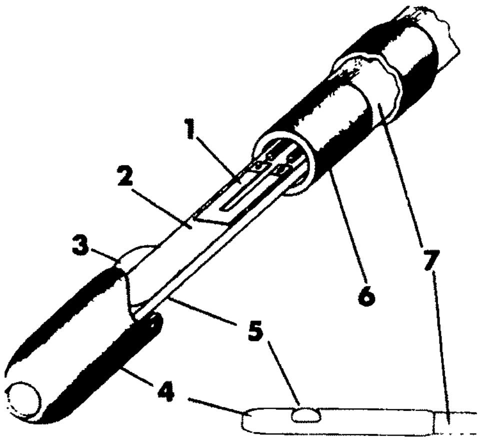


Figure 1. Enlarged view of the needle force probe. 1 = strain gauge; 2 = flexible bar; 3 = promontory in the window part of the flexible bar; 4 = outer tube; 5 = lateral window; 6 = bar support; 7 = PE-catheter. Reproduced with permission from J.L. Theissen et al.: "Local Forces in the myocardium." Br J Anaesth. 1988; 60:72S–77S.

tensions. A femoral artery catheter, a central venous catheter and a balloon–tipped flow directed thermodilution pulmonary arterial catheter were inserted. Left thoracotomy and pericardiotomy were performed. A Millar Mikro–Tip Catheter Pressure Transducer (Millar Instruments Inc., Houston, Tex) was inserted into the left ventricle through the apex of the heart. Three needle force probes, 1.2 mm in diameter and 9 mm long (Ergopuls, Stroh Magstadt) as shown in Figure 1, were implanted into the left ventricular wall parallel to the epicardial surface (12,13). Two of these were implanted into superficial layers of the myocardium and the other one into midwall layers. The pericardium was closed. A thoracic drainage tube was placed and the chest wall closed. Body temperature was measured by a rectal probe and maintained between 36 and 38°C by means of heating lamps. Heart rate (HR), systemic arterial pressures, right atrial pressure (RAP), pulmonary artery pressure (PAP), left ventricular pressure (LVP), and the signals generated by the needle force probes were recorded continuously. Pulmonary capillary wedge pressure (PCWP) was recorded intermittently and cardiac output (CO) was measured in duplicate using the thermodilution technique with 5 mL iced saline. Mean arterial pressure (MAP) and systemic vascular resistance (SVR) were calculated using standard formulae (14).

After the preparation, a 3- to 4-hr stabilization period was allowed before baseline measurements were taken. Propofol, 2.5 mg/kg, or etomidate, 0.3 mg/kg, were given in a randomized, cross–over sequence via central venous line over 30 sec. Hemodynamic parameters were measured 1, 3, 5, and 10 min after the administration of the first drug. Ninety minutes after all parameters had returned to baseline levels the second drug was given. Again, all hemodynamic and cardiodynamic values were measured 1, 3, 5, and 10 min after drug administration.

Mean values and standard error of the mean were calculated for each measurement. Statistical analysis was done using the Friedman test and $P < 0.05$ was considered statistically significant.

Results

The entire experiment was performed under basal anesthesia maintained by nitrous oxide and the continuous infusion of ketamine and fentanyl.

No significant differences could be seen between the baseline values of the two groups. The hemodynamic responses during the first ten minutes after the injection of either propofol, 2.5 mg/kg, or etomidate, 0.3 mg/kg, are summarized in Table 1. Propofol caused significant reductions in systolic (SAP, 19.9%) and diastolic (DAP, 25.3%) arterial pressures as well as in MAP (22.8%). The greatest decrease in MAP (22.8%) was observed one minute after the administration of propofol. Thereafter arterial pressure showed a slight tendency to increase. With etomidate, systemic arterial pressure was not changed. In the propofol treated animals HR decreased at 5 and 10 min. The small decrease in HR that occurred with etomidate was not significant.

A decrease in CO to its lowest level from 5.2 ± 0.3 L/min to 4.3 ± 0.4 L/min was observed when propofol was given. This decrease of 17.3% was not statistically significant. However, more important than mean values were the changes in individual animals. In Figure 2 it can be seen that propofol caused a sudden decrease in CO in 6 of the 8 animals. In one animal CO decreased by more than 50%. The increase in CO in another animal was caused by a marked increase in HR of unknown origin. Etomidate had no influence on CO. The moderate 11.6% decrease in SVR one minute after propofol was not seen with etomidate. PCWP did not change in either group.

Two types of force signals were generated by the needle force probes within the myocardium. Figure 3 shows the typical implantation sites and the resulting signals of the force probes. The afterloaded–type increases during the ventricular ejection period. In histological preparations of previous experiments, this type of force signal was found to originate from areas where the force probe was coupled to oblique transmural fibers (13,15,16). These fibers are espe-

Table 1. Hemodynamic Changes During the First 10 Min After the Injection of Either Propofol 2.5 mg/kg or Etomidate 0.3 mg/kg

	Baseline	1 min	3 min	5 min	10 min
PROPOFOL					
SAP (mm Hg)	120.9 ± 7.0	96.9 ± 6.4*	100.6 ± 7.1*	103.3 ± 7.3	104.5 ± 7.6
DAP (mm Hg)	80.4 ± 6.6	60.1 ± 4.4*	65.4 ± 5.1*	68.1 ± 4.7	69.9 ± 4.8
MAP (mm Hg)	93.3 ± 6.5	72.1 ± 5.2*	77.3 ± 5.6*	79.4 ± 5.6	81.1 ± 5.7
HR (beats/min)	114.4 ± 5.9	110.4 ± 6.8	109.6 ± 7.4	104.9 ± 8.2*	105.6 ± 7.6*
CO (L/min)	5.2 ± 0.3	4.3 ± 0.4	4.4 ± 0.4	4.5 ± 0.4	4.5 ± 0.4
SVR (dyn s cm^{-5})	1297 ± 125	1147 ± 136	1246 ± 146	1238 ± 147	1305 ± 152
PCWP (mm Hg)	10.0 ± 0.6	9.5 ± 0.7	9.9 ± 0.8	9.8 ± 0.8	9.8 ± 0.8
ETOMIDATE					
SAP (mm Hg)	121.5 ± 7.2	120.6 ± 7.9	121.5 ± 7.9	120.9 ± 7.3	120.5 ± 6.8
DAP (mm Hg)	80.0 ± 5.5	79.3 ± 5.0	79.8 ± 6.2	80.1 ± 6.1	81.6 ± 5.1
MAP (mm Hg)	93.9 ± 5.2	93.1 ± 5.6	93.5 ± 6.3	93.6 ± 5.9	94.4 ± 5.1
HR (beats/min)	117.0 ± 7.1	113.5 ± 6.4	112.0 ± 6.0	111.5 ± 6.5	113.8 ± 6.1
CO (L/min)	5.2 ± 0.3	5.0 ± 0.2	5.1 ± 0.3	5.2 ± 0.3	5.4 ± 0.5
SVR (dyn s cm^{-5})	1282 ± 104	1285 ± 86	1266 ± 111	1256 ± 97	1284 ± 151
PCWP (mm Hg)	9.1 ± 0.6	10.1 ± 0.6	10.1 ± 0.8	10.3 ± 0.6	10.0 ± 0.9

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; SVR = systemic vascular resistance; PCWP = pulmonary capillary wedge pressure; (n = 8), mean ± SEM, *P < 0.05.

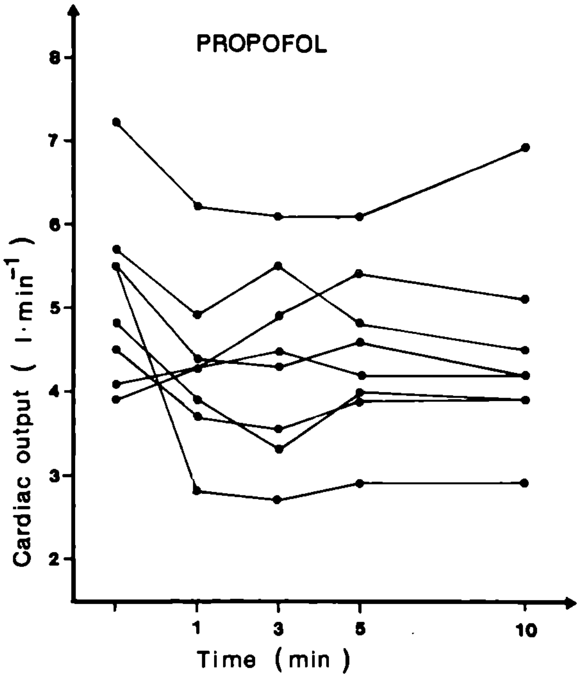


Figure 2. Cardiac output during the first 10 min after the injection of propofol 2.5 mg/kg.

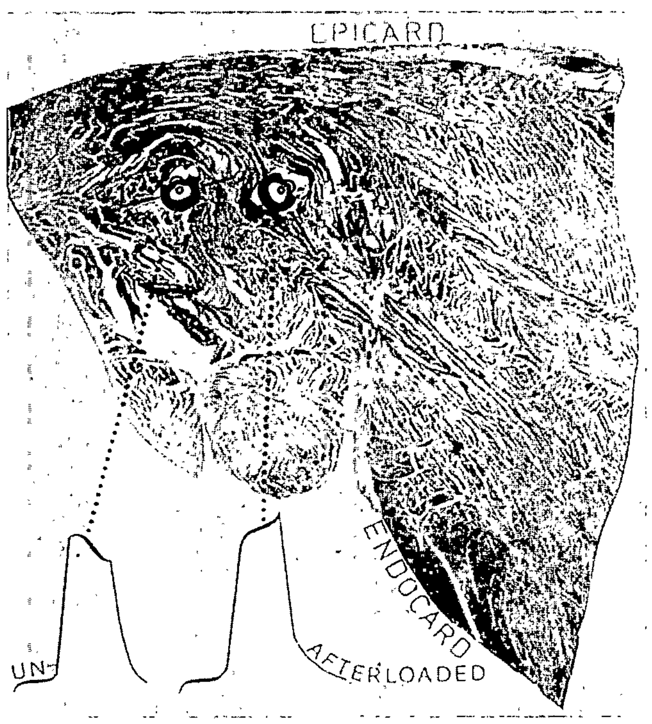


Figure 3. Implantation sites of the needle force probes; afterloaded signals are generated when the probe is coupled to oblique transmurally orientated fibers (2); unloaded signals emerge from areas where the fiber orientation is parallel to the ventricular surface (1). Reproduced with permission from J.L. Theissen et al.: "Local Forces in the myocardium." Br J Anaesth. 1988;60:72S–77S.

cially sensitive to geometric alterations of the heart (15,16). The unloading force signal decreases in force during ventricular ejection. This type of force signal was previously found when surfaceparallel fibers in the epicardium surrounded the probe. Variations of this latter force type paralleled left ventricular pressure alterations in earlier experiments (13,15–17). Left ventricular force (LVF) was determined as the amplitude of the generated signals. The early systolic rates of increase in force (force velocity rise index; dF/dt max) was derived from the force signals by

Table 2. Cardiodynamic Changes During the First 10 Min After the Injection of Either Propofol 2.5 mg/kg or Etomidate 0.3 mg/kg

	Baseline	1 min	3 min	5 min	10 min
PROPOFOL					
LVP_{sys} (mm Hg)	111.9 ± 6.0	92.3 ± 5.6*	91.8 ± 4.9*	97.5 ± 6.8	97.9 ± 5.3
LVF (% of Baseline)	100.0	83.7 ± 4.0*	87.7 ± 3.5*	87.2 ± 3.6*	87.5 ± 2.8*
dF/dt max (% of Baseline)	100.0	76.5 ± 4.9*	80.0 ± 5.7*	83.9 ± 6.0	82.9 ± 6.4
ETOMIDATE					
LVP_{sys} (mm Hg)	110.3 ± 4.8	109.1 ± 4.7	107.6 ± 5.7	108.3 ± 4.1	111.1 ± 4.0
LVF (% of Baseline)	100.0	98.0 ± 0.8	95.9 ± 2.4	94.5 ± 2.8	98.1 ± 1.2
dF/dt max (% of Baseline)	100.0	99.6 ± 2.8	94.6 ± 2.5	95.5 ± 1.8	99.8 ± 2.1

LVP_{sys} = systolic left ventricular pressure; LVF = left ventricular force; dF/dt max = early systolic rates of increase in force; ($n = 8$), mean ± SEM, $^*P < 0.05$.

determining the maximum slope of the generated signal.

Data on LVF and dF/dt max are not presented in absolute values but as percents of baseline values of the amplitude (LVF) or slope (dF/dt max) of the force signals. The effects of propofol, 2.5 mg/kg, and etomidate, 0.3 mg/kg, on cardiodynamics are shown in Table 2. The decrease in systemic arterial pressure produced by propofol was paralleled by a significant (17.6%) reduction in systolic left ventricular pressure (LVP_{sys}) below baseline levels. Analysis of the unloading–type force probe signals showed a 16.3% decrease ($P < 0.05$) in LVF below baseline levels one minute after propofol with only a mild subsequent increase. Etomidate did not alter LVP_{sys} or LVF. Even more pronounced was the effect of propofol on dF/dt max. In contrast to etomidate, propofol was associated with a significant 23.5% reduction in dF/dt max with only a slight tendency to recover. The afterloaded type of force curve showed only minor changes. It can be assumed that the geometry of the ventricle did not change with either drug.

Discussion

Nitrous oxide, ketamine, and fentanyl were given throughout the present experiments. We therefore cannot exclude that these agents modified the hemodynamic or cardiodynamic alterations associated with propofol and etomidate. However, because baseline measurements as well as all measurements after the administration of propofol or etomidate were made under equal anesthetic conditions, it seems likely that the observed changes can be ascribed to either of the two drugs that were added.

Comparisons of intravenous anesthetic agents require the use of equipotent doses. A study comparing the effects of different doses of propofol and etomidate in dogs does not exist. Grounds et al. (18) found the relative potency of propofol compared to thiopental to be 1:1.6 in humans (inducing sleep in patients). This corresponds to doses of propofol 2.5 mg/kg and thiopental 4.0 mg/kg. Kissin and colleagues (19) studied the potencies of etomidate and propofol in dogs. They reported equianesthetic doses (doses blocking movement response to noxious stimuli) to be 1.4 mg/kg for etomidate and 15.5 mg/kg for thiopental. If the relation of doses for etomidate, thiopental and propofol recommended for induction of anesthesia in humans (0.3 mg/kg, 4.0 mg/kg, and 2.5 mg/kg, respectively) are compared, they are in close agreement with those reported by Grounds (18), Kissin (19), and co–authors. Although these reports do not compare the same anesthetic level in one species, their results suggest that 0.3 mg/kg of etomidate and 2.5 mg/kg of propofol may be equipotent in dogs.

Rapid and significant decreases in systemic arterial pressures produced by propofol. 2.5 mg/kg, were not seen with etomidate, 0.3 mg/kg. The decrease in MAP associated with propofol by 22.8% was paralleled by a 17.6% decrease in systolic LVP. In combination with a 11.6% reduction in SVR, CO decreased 17.3% and HR slowed 3.5%. Similar reductions in MAP produced by propofol were reported by Grounds et al. (5) and Fahmy (6) et al. using 2.5 mg/kg of propofol, and by Claeys (7), Coates (8), Monk (9), and coworkers with an induction dose of propofol, 2.0 mg/kg, followed by an infusion of propofol. The degree of hypotension reported in association with propofol is variable. Patrick et al. (10) observed a 25% decrease in MAP with a smaller induction dose (1.5 mg/kg of propofol) in heavily premedicated patients with ischemic heart disease, all of whom were receiving beta-receptor blocking agents. Stephan et al. (20) reported only a 15.0% decrease in MAP with propofol, 2.0 mg/kg, in patients with ischemic heart disease on treatment with calcium antagonists or beta-receptor blocking agents and nitrates. These variations may be due to differences in technique, experimental conditions, prestudy drug therapy, premedication, concomitant drug administration, and preexisting cardiovascular disease. However, even in a single study, a wide range of responses in cardiovascular parameters could be observed (9).

Different reasons have been suggested for the decrease in MAP associated with propofol. Fahmy (6), Claeys (7), Patrick (10), Profeta (21), and associates found significant decreases in SVR with little change in CO. On the other hand, significant decreases in CO with little change in SVR were seen by Van Aken (22), Williams (23), Stephan (20), and coworkers. However, as in the present study, most investigators found the combination of a reduction in CO and SVR to be responsible for the decrease in MAP (5,7–9,24,25). The variation in the degree of reported hemodynamic alterations may be explained partly by the additional use of nitrous oxide and its cardiovascular effects. The observed decrease in SVR associated with the reduction in MAP due to propofol may be the result of a direct effect of the drug on vascular smooth muscle, or represent an alteration in baroreceptor activity that would otherwise lead to an increase in sympathetic nervous outflow. A similar interference with baroreceptors was reported by Cullen et al. (26). In their study, propofol caused a resetting of baroreceptors to allow a slower HR despite decreased arterial pressures. The absence of a reflex tachycardia in our study may most likely be caused by this phenomenon, but an additional influence of nitrous oxide or fentanyl cannot be excluded. Al Khudhairi et al. (27) reported a significant increase in HR associated with the induction of anesthesia with propofol in patients with ischemic heart disease. The reason for the increase in HR is unclear and even somewhat surprising since all patients were treated with beta-blocking agents. The increase may be attributed in part to an increase in $PaCO_2$.

The absence of an increase in HR associated with etomidate in this study is not surprising. In contrast to the majority of intravenous induction agents, Bruckner et al. (28) found that etomidate does not necessarily lead to an increase in HR.

Changes in CO may be caused by alterations in preload, afterload, HR, and myocardial contractility. In the present data, the 17.3% reduction in CO in the presence of an unchanged preload and HR and a reduced SVR, strongly suggests a negative inotropic effect for propofol. Such a reduction in myocardial contractility was supported by the data derived from the signals of the implanted force probes. The data showed a statistically significant 16.3% decrease in LVF and a significant 23.5% reduction in dF/dt max. The reduction of systolic maxima of contraction may be explained by a reduction of afterload, but the decrease in dF/dt max with an almost unchanged HR and preload can only represent a negative inotropic effect of propofol.

The reduction in SVR without a decrease in RAP or PCWP suggests that the vasodilating effect of propofol involves mainly arteries and arterioles rather than capacitance vessels. Therefore early intravenous infusion of electrolyte solution to reduce the decrease in MAP by increasing the myocardial fiber tension is not likely to be effective. This seems to be of even greater importance as propofol blocks potential compensation associated with an increase in HR.

The absence of a reflex tachycardia associated with the administration of propofol may be considered beneficial in that there is no associated increase in myocardial oxygen consumption. However, a stable heart rate accompanied by decreases in CO and SVR that cause a significant decrease in MAP may result in inadequate peripheral perfusion pressure and inadequate oxygen delivery. Whether the decrease in contractility that was observed in the present study is a direct effect of propofol on cardiac muscle or the result of a mismatch in oxygen supply and oxygen consumption is unknown. Propofol therefore should be used with care in patients with coronary artery disease, in hypovolemic patients, and in cases where an additional cardiodepressant drug might be added.

References

1. Cummings GC, Dixon J, Kay NH, Windsor JPW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK. Dose requirements of ICI 35868 (propofol, 'Diprivan'), a new formulation for induction of anaesthesia. Anaesthesia 1984;39:1168–71.
2. Glen JB, Hunter SC. Pharmacology of an emulsion formulation of ICI 35868. Br J Anaesth 1984;56:617–26.
3. Kay NH, Uppington J, Sear JW, Allen MC. Use of an emulsion of ICI 35868 (propofol) for the induction and maintenance of anaesthesia. Br J Anaesth 1985;57:736–42.
4. Nightingale P, Healy TEJ, Hargreaves J, McGuiness K, Kay B. Propofol in emulsion formulation. Induction characteristics and venous sequelae. Eur J Anaesthesiol 1985;2:361–68.
5. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. Anaesthesia 1985;40:735–40.

6. Fahmy NR, Alkhouli HM, Sunder N, Smith D, Kelly MM. Diprivan: A new intravenous induction agent. A comparison with thiopental. Anesthesiology 1985;63:A363.
7. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988;60:3–9.
8. Coates DP, Monk CR, Prys-Roberts C, Turtle M, Spelina KR, Norley I. Hemodynamic effects of the infusion of the emulsion of propofol during nitrous oxide anesthesia in humans. Anesth Analg 1987;66:64–70.
9. Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina KR. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Studies in association with peripheral arterial surgery. Br J Anaesth 1987;59: 954–60.
10. Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol ('Diprivan') and thiopentone in patients with coronary artery disease. Postgrad Med J 1985;61(Suppl.3):23–7.
11. Coates DP, Prys-Roberts C, Spelina KR, Monk CR, Norley I. Propofol ('Diprivan') by intravenous infusion with nitrous oxide: dose requirements and haemodynamic effects. Postgrad Med J 1985;61(Suppl.3):76–9.
12. Lunkenheimer PP, Graham G, Stroh N, Welham K, Scharsich M. Assessment of local force in the myocardium disproving the distinctness of contractility parameters derived from left ventricular pressure. Eur Surg Res 1976;8:104–5.
13. Theissen JL, Lunkenheimer PP, Redman K, Frieling G, Stroh N, Lunkenheimer A. Local forces in the myocardium. Br J Anaesth 1988;60:72S–7S.
14. Kappagoda CT, Linden RJ. The use of SI units in cardiovascular studies. Cardiovasc Res 1976;10:141–8.
15. Lunkenheimer PP, Lunkenheimer A, Torrent-Guasp F. Kardiodynamik: Wege zur strukturgerechten Analyse der Myocardfunktion. In: Zolch KA, ed. Beiträge zur Kardiologie. Perimed Fachbuch-Verlagsgesellschaft, Erlangen, 1985;33:106–29.
16. Lunkenheimer PP, Stroh N, Scharsich M, Koubenec J, Schmuziger M, Achatzky R, Dittrich H, Welham K, Graham G. Continuous assessment of myocardial force during heart surgery. Curr Top Crit Care Med 1977;3:28–38.
17. Lunkenheimer PP, Lunkenheimer A, Stroh N, Kohler F, Welham K, Graham G, Kirk E, Sonnenblick EH, Kroller J. Vergleich klassischer und neuer methodischer Zugänge zum intramyocardialen Kraftverteilungsmuster. Zentralblatt für Veterinärmedizin 1982;A29:557–601.
18. Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. Eur J Anaesthesiol 1986;3:11–7.
19. Kissin I, Motomura S, Aultman DF, Reves JG. Inotropic and anesthetic potencies of etomidate and thiopental in dogs. Anesth Analg 1983;62:961–5.
20. Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta HJ. Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. Br J Anaesth 1986;58:969–75.
21. Profeta JP, Guffin MMS, Mikula RN, Dolman J, Kaplan JA. The hemodynamic effects of propofol and thiamylal sodium for induction in coronary artery surgery. Anesth Analg 1987; 66:S142.
22. Van Aken H, Meinshausen E, Prien T, Brüssel T, Heinecke A, Lawin P. The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N_2O in humans. Anesthesiology 1988;68:157–63.
23. Williams JP, McArthur JD, Walker WE, Teunissen E, Rietsema K, Stanley TH. The cardiovascular effects of propofol in patients with impaired cardiac function. Anesth Analg 1986; 65:S166.
24. Aun C, Major E. The cardiorespiratory effects of ICI 35868 in patients with valvular heart disease. Anaesthesia 1984; 39:1096–100.
25. Prys-Roberts C, Davies JR, Calverley RK, Goodman NW. Haemodynamic effects of infusions of diisopropylphenol (ICI 35868) during nitrous oxide anaesthesia in man. Br J Anaesth 1983;55:105–11.
26. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987;66:1115–20.
27. Al-Khudhairi D, Gordon G, Morgan M, Whitwam JG. Acute cardiovascular changes following disoprofol. Effects in heavily premedicated patients with coronary artery disease. Anaesthesia 1982;37:1007–10.
28. Bruckner JB, Gethmann JW, Patschke D, Tarnow J, Weymar A. Investigations in the effect of etomidate on the human circulation. Anaesthesist 1974;23:322–30.

ANESTH ANALG
1989;69:41–5

Penile Block via the Subpubic Space in 100 Children

Bernard Dalens, MD, Guy Vanneuville, MD, and Pierre Dechelotte, MD

DALENS B, VANNEUVILLE G, DECHELOTTE P. Penile block via the subpubic space in 100 children. Anesth Analg 1989;69:41–5.

A technique for blocking the dorsal nerves of the penis was designed after reevaluation of the gross anatomy of the subpubic space and penis in children. The technique consists of inserting a short bevel needle in the two compartments of the subpubic space, where the nerves run before entering the base of the penis, and of injecting a small volume (0.1 mL/kg of body weight) of local anesthetic. This two-puncture procedure was prospectively evaluated in 100 children undergoing surgery of the penis under light general anesthesia. The local anesthetic was a solution of 1% lidocaine (Group A) or 0.5% bupivacaine (Group B). The technique did not require any special skill and was successful in all patients. In four cases, the block needle was withdrawn and reinserted due to venous blood reflux. No complications occurred and anesthesia was satisfactory for completion of surgery. The duration of postoperative pain relief was significantly longer in patients given bupivacaine than in those given lidocaine. It is concluded that the subpubic approach to the dorsal nerves of the penis is easy, safe, and reliable, and that 0.5% plain bupivacaine provides long-lasting postoperative pain relief.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—penile block. ANESTHESIA—pediatric.

Superficial operations on the penis, especially circumcision, usually cause severe postoperative pain. Several anesthetic techniques have been described for providing satisfactory anesthesia, but penile block appears the most dependable technique because it is a peripheral procedure aimed at blocking the nerves that supply sensory innervation to the foreskin and glans. Basically, penile block consists of piercing at the base of the penis the penile fascia (Buck's fascia) under which run the dorsal nerves of the penis and injecting the local anesthetic there (1,2). However, Buck's fascia is tightly attached to the corpora cavernosa, and our anatomical studies showed that it was virtually impossible to pierce the fascia without penetrating the corpora cavernosa.

We reevaluated the gross anatomy and relations of the dorsal nerves of the penis on cadavers of children and found that these nerves could be more safely approached via the subpubic space, as reported by Brown and Schulte-Steinberg (3), rather than via the almost potential space lying between the penile fascia and the corpora cavernosa. Based on these anatomical considerations, a two-puncture technique was prospectively evaluated on 100 pediatric patients undergoing surgery of the foreskin and glans. The study protocol received institutional approval.

Methods and Materials

Anatomic Considerations

The ilioinguinal and genitofemoral nerves contribute some fibers to the skin covering the base of the penis, but sensory innervation of the penis is mainly provided by the two dorsal nerves of the penis that are terminal branches of the pudendal nerves. The pudendal nerves originate from the sacral plexus, deriving their fibers from the 2nd to the 4th sacral spinal nerves (Figure 1). At the distal part of the pudendal canal where they run into the ischial fossa, the pudendal nerves give off the inferior hemorrhoidal nerve and then divide into their two terminal branches: 1) the perineal nerve, which supplies the scrotum and several perineal muscles and 2) the dorsal nerve of the penis (dorsal nerve of the clitoris in the female).

The dorsal nerves of the penis pass under the pubic bone through the substance of the suspensory ligament of the penis (fundiform ligament) and then run immediately lateral to the dorsal artery of the penis at the inner aspect of the penile fascia (Buck's fascia), close to the corpora cavernosa. After their

---

Received from the Departments of Anesthesiology, Anatomy, and Pathology, Hôtel-Dieu Hospital, Clermont-Ferrand, France. Accepted for publication January 13, 1989.

Address correspondence to Dr. Dalens, Pavillon Gosselin, Hôtel-Dieu B. P. 69, 63003 Clermont-Ferrand, France.

©1989 by the International Anesthesia Research Society

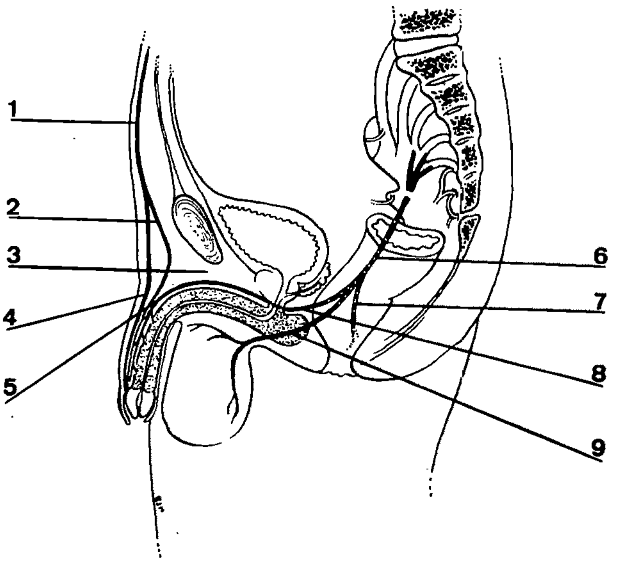


Figure 1. Gross anatomy of the pudendal nerve and its division branches: 1) Superficial fascia of the abdominal wall; 2) Deep layer of the superficial fascia of the abdominal wall (Scarpa's fascia); 3) Subpubic space; 4) Superficial layer of the superficial fascia of the abdominal wall; 5) Penile fascia (Buck's fascia); 6) Pudendal nerve; 7) Inferior hemorrhoidal nerve; 8) Dorsal nerve of the penis; 9) Perineal nerve.

emergence from under the pubic bone, the dorsal nerves are enclosed in a fat-filled space, poorly described in textbooks of anatomy, the subpubic space (Figure 2). The subpubic space is roughly dihedral and its boundaries are above and posteriorly, the public bone and the perineal membrane; below and posteriorly, the horizontal part of the corpora cavernosa covered by a fibrous envelope (continuous with Buck's fascia at the neck of the penis); anteriorly: 1) the deep layer (also termed Scarpa's fascia) of the superficial fascia of the abdominal wall (fascia superficialis) which contributes medially to the fundiform ligament (Figure 2) and is continuous with Buck's fascia, then 2) the superficial layer of the superficial fascia, and then 3) the skin covering the pubic area. The superficial layer of the fascia superficialis is thick but areolar and loosely packed, whereas the deep layer (Scarpa's fascia) is membranous and contains elastic fibers.

The subpubic space is usually divided at midline, within the substance of the suspensory ligament of the penis, in two non-communicating compartments (Figure 3). Therefore a single puncture technique is not suitable for blocking the two dorsal nerves of the penis at the level of the subpubic space.

Patients

One hundred ASA 1 male children scheduled for operations on the penis were selected after informed consent had been obtained from parents and, as often as possible, from the children themselves. The patients ranged in age from 3 months to 16 years (5.3 ± 3.4 years) and the main indications for surgery were: phimosis (49 patients), ritual circumcision (30 patients, all Muslims), hypospadias repair (15 patients, including 11 with glandular and 4 with penile hypospadias), paraphimosis (3 patients), biopsies of the glans and foreskin (2 patients), and traumatic wound of the penis (1 patient).

Methods

Anesthetic methods. All procedures were carried out in operating rooms under light general anesthesia (without tracheal intubation) after insertion of a peripheral venous line, as is usual in our unit for regional block procedures in children (4,5). Anesthesia was maintained with use of 0.25–0.5% halothane in 65% N_2O/35% O_2.

We used 30-mm short beveled 23-gauge needles designed at our specifications by Eugédia™ (France) for caudal block (6). Two anesthetic solutions free of epinephrine were used: 1% lidocaine in the first 50 patients (Group A) and 0.5% bupivacaine in the remaining 50 (Group B). These solutions were administered on a weight basis: 0.1 mL/kg for each injection, thus accounting for a 0.2 mL/kg total volume (i.e., 2 mg/kg for lidocaine and 1 mg/kg for bupivacaine).

The subpubic approach to the dorsal nerves of the penis. The patients were placed supine in the dorsal recumbent position. The landmarks were: 1) the symphysis pubis and 2) the inferior ramus of the pubic bone from both sides. Two sites of puncture were marked on the skin 0.5 (infants) to 1 cm (older children) lateral to the symphysis pubis and immediately below the right and left inferior rami of the pubic bone (Figure 4 A).

The base of the penis was gently pulled down (to favor bending of Scarpa's fascia). The block needle was then inserted and advanced posteriorly at a 70–80° angle to the skin, slightly medially and caudally (approximately 10–20° in the two directions) (Figure 4 B). After a first (smooth) "give" was felt as the superficial layer of the superficial fascia of the abdomen was pierced, the needle was advanced until another (more marked) "give" was felt when Scarpa's fascia was crossed as the tip of needle entered the subpubic space. The solution of local anesthetic was then injected slowly after aspiration tests.

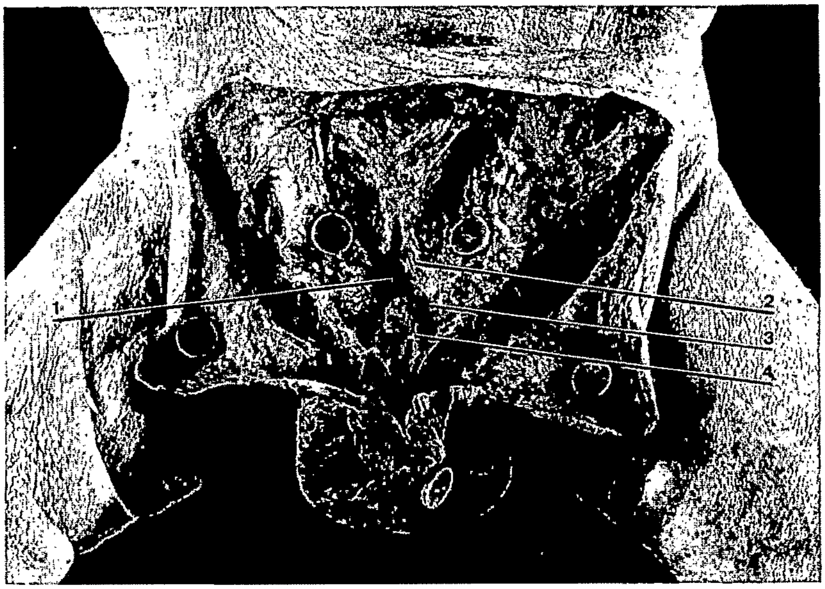


Figure 2. Gross anatomy of the subpubic space. (The right parts of the fundiform ligament and Scarpa's fascia have been removed). 1) Right compartment of the subpubic space (uncovered); 2) Fundiform ligament; 3) Scarpa's fascia (deep layer of the superficial fascia of the abdominal wall); 4) Corpora cavernosa (covered by Buck's fascia).

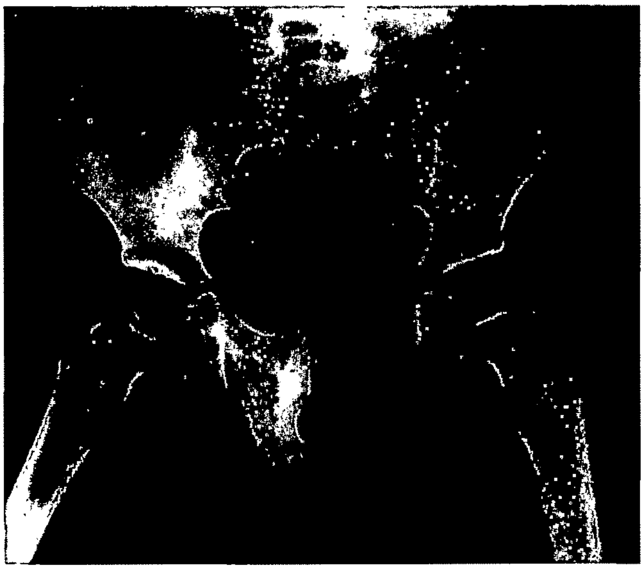


Figure 3. Spread of a solution containing contrast media in the right part of the subpubic space. Note the lack of diffusion toward the left part of the subpubic space.

The same procedure was then performed at the second site, and 15 minutes were allowed for establishment of the sensory block before surgery began.

Monitoring procedures and evaluation of anesthesia. Electrocardiogram tracings, respiratory rate, blood pressure (Dinamap), tidal volume, and end-tidal CO_2 were monitored during the procedures. The penile block was considered successful when the scheduled operation was achieved without any additional treatment (intravenous narcotics, increased concentrations of halothane, or intravenous sedatives). The extent of analgesia was evaluated after completion of surgery by skin pinching. Duration of the sensory block was measured as the time between injection and the first evidence of pain (complaints of pain, crying, grimacing, episodes of restlessness). Most patients were discharged after the 6th postoperative hour or after their first spontaneous micturition. All patients were re-examined the day after surgery.

Statistical methods. Results, expressed as mean ± SD, were analyzed using Mann-Whitney test. Qualitative parameters were evaluated using chi-square test.

Results

The block procedure was successful in all patients, and no additional treatment was required for completion of surgery. In four patients (two in each group), venous blood reflux occurred. The needle was then withdrawn and reinserted without further vascular penetration before injection. The depth at which the block needle was inserted varied from 8–30 mm and was not correlated to patient's age or weight.

The anesthetized area included all the structures of the penis except the skin covering its base, whereas the scrotum remained unaffected. All the patients of Group A experienced pain 3–6 hours (4.2 ± 1.2 hours) after the injection of lidocaine, whereas only two patients given bupivacaine produced evidence of pain 5 and 6 hours, respectively, after they had been returned to their bed. The remaining 48 patients of Group B did not complain of pain during the first 24

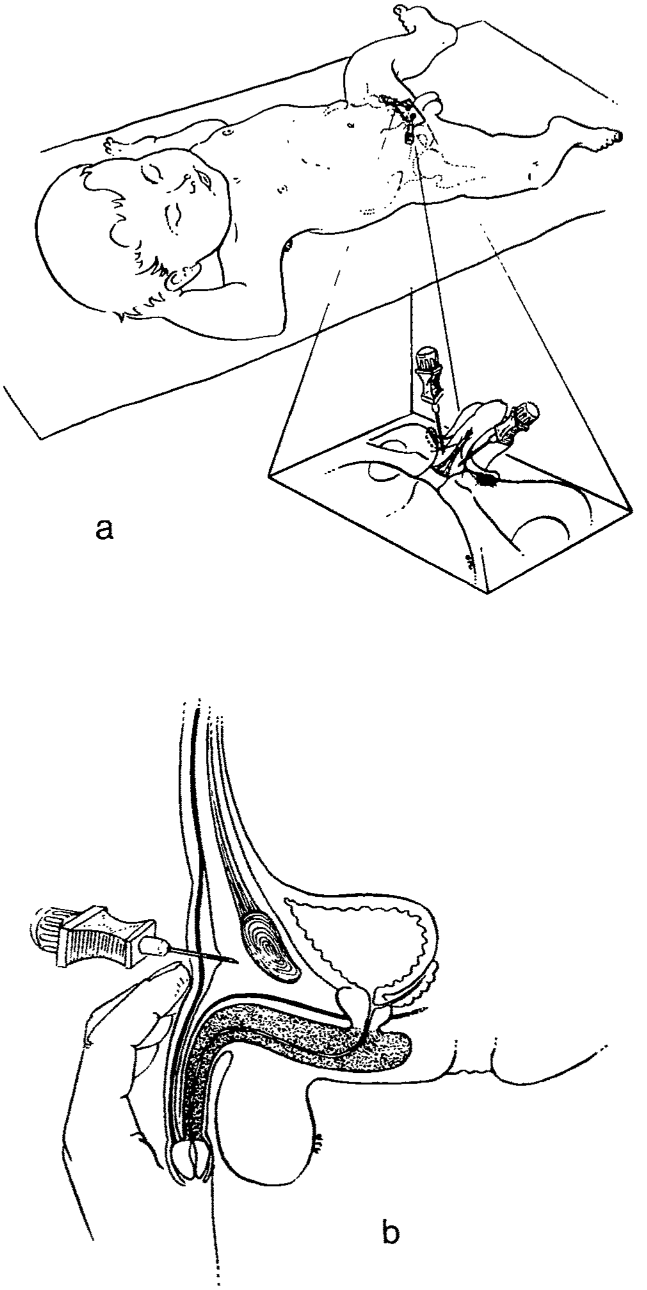


Figure 4. Blocking procedure. **A**, Landmarks and sites of puncture. **B**, Technique. Note the finger pulling down gently the base of the penis.

hours. The difference between the two groups is statistically significant ($P < 10^{-6}$).

The first spontaneous micturition was slightly, but not significantly, delayed in Group B (4.5 ± 1.9 hr; extreme values: 1.5 to 7.5 hr) as compared with Group A (3.5 ± 2.1 hr; extreme values: 0.5 to 7.5 hr). No complications occurred, and the only adverse effect was in a 6-yr-old patient of Group A who complained of headache for 3 hr following the operation.

Discussion

Postoperative pain after operations on the penis of young patients is perhaps particularly a problem because the surgical procedure itself is frequently minor (cure of phimosis, circumcision), whereas the pain produced is both severe and long-lasting. Numerous anesthetic techniques have been recommended, including administration of parenteral narcotics (7–9), caudal block (9–11), subcutaneous ring block at the base of the penis (12,13), topical anesthesia (14,15), and dorsal nerve block (1,2,10,14,16,17). Parenteral narcotics do not always guarantee appropriate postoperative pain relief (6,8). Caudal blocks are very effective, but performing a central block for minor surgery is controversial, and adverse effects such as vomiting and delayed micturition are not unusual (10). Topical anesthesia with use of any of the available preparations of lidocaine (ointment, spray, jelly) is simple, can be repeated, and is apparently safe (but systemic absorption has not been evaluated); however, persistence of mild or moderate pain is not unusual (14,15), and bacterial contamination of the surgical wound may result from repeated applications because "touching of the wound during the application is usually unavoidable" (15). Blocking the dorsal nerves of the penis, either at random by a "subcutaneous" ring of local anesthetic (12,13) or more accurately by a specific block procedure (1,2) appears more logical. Blind injections of a "small" volume of local anesthetic (bupivacaine), especially dorsally in the midline, may damage the dorsal vessels of the penis, with potential risks of compressive hematomas and systemic toxicity.

Dorsal nerve block as described by Soliman and Trembley (1) is technically difficult. The procedure requires considerable skill and, in a number of patients, surgical anesthesia is not obtained (1,10,16). Furthermore, the procedure may lead to complications as severe as gangrene of the glans penis (18). In our opinion, on the basis of our anatomical studies, the dorsal nerves of the penis should not be approached at the level of the penis.

Approaching the nerves from within the subpubic space is anatomically rational and our prospective study has proved its reliability in 100 consecutive patients. The technique is simple and free of danger to any important structures. Furthermore, due to the size and limits of the subpubic space, vascular is virtually impossible, even if a large volume is injected. However, because there is usually a medial division of this space, a single puncture technique within the suspensory ligament (3) will not predictably provide satisfactory anesthesia. The two-puncture procedure reported previously specifically blocks the dorsal nerves of the penis, whereas the area supplied by the perineal nerves (the other terminal branches of the pudendal nerves) remains unaffected.

Both anesthetic solutions used in this study were suitable. However, bupivacaine should be preferred because it provides significantly longer relief of postoperative pain. As in our series, Carlsson and Swenson (16) reported that most children undergoing circumcision after penile blocks with 0.25% bupivacaine did not require analgesics during the first 24 hr postoperatively. The time to the first spontaneous micturition was not significantly influenced by the local anesthetic used and voiding occurred significantly earlier after dorsal nerve block, as is usually reported, than after caudal blocks (6,10).

The depth to which the needle was inserted to penetrate the subpubic space varied widely and was not influenced by patient's age. This is due to the especially large fat content of the subcutaneous pubic area in infants. In addition, the subcutaneous tissue in the pubic area is less densely packed in young patients than in older ones; this may facilitate the displacement of the deep layer of the fascia superficialis before it is pierced by the tip of the block needle. A thin, long beveled needle might penetrate the subpubic space at a shorter distance from the skin, but, as reported after caudal blocks (6), this may result in an increased risk of vascular penetration. Therefore, we believe that short bevel needles as we use for caudal blocks are preferable.

In summary, injecting a small volume of local anesthetic, preferably plain bupivacaine, in the two compartments of the subpubic space uniformly resulted in block of the two dorsal nerves of the penis. The procedure does not require special skill and complications are unlikely for anatomical reasons. We believe that the subpubic approach to the dorsal nerve of the penis is easy, safe, and reliable, and that it can be recommended for operations of the penis (except at its base) in children.

We thank Professor Ven Murthy, Laval University, Québec, Canada for considerable help in reviewing this manuscript and J. P. Monnet and Y. Harmand for technical assistance in the preparation of illustration.

References

1. Soliman MG, Tremblay NA. Nerve block of the penis for postoperative pain relief in children. Anesth Analg 1978; 57:495–8.
2. Bacon AK. An alternative block for post-circumcision analgesia. Anaesth Intensive Care 1977;5:63–4.
3. Brown TCK, Schulte-Steinberg O. In: Cousins MJ, Bridenbaugh PO, eds. Neural Blockade in Clinical Anesthesia and Management of Pain, 2nd ed. Philadelphia: JB Lippincott, 1988:669–94.
4. Dalens B, Vanneuville G, Tanguy A. A new parascalene approach to the brachial plexus in children: comparison with the supraclavicular approach. Anesth Analg 1987;66:1264–71.
5. Dalens B, Tanguy A, Vanneuville G. Lumbar plexus block in children: a comparison of two procedures in 50 patients. Anesth Analg 1988;67:750–8.
6. Dalens B, Hasnaoui A. Caudal anesthesia in pediatric surgery: success rate and adverse effects in 750 consecutive patients. Anesth Analg 1989 (in press).
7. Shulman J, Ben-Hur N, Neuman Z. Surgical complications of circumcision. Am J Dis Child 1964;107:149–54.
8. Martin LVH. Postoperative analgesia after circumcision in children. Br J Anaesth 1982;54:1263–6.
9. Blaise G, Roy WL. Postoperative pain relief after hypospadias repair in pediatric patients: regional analgesia versus systemic analgesics. Anesthesiology 1986;65:84–6.
10. Vater M, Wandless J. Caudal or dorsal nerve block?—A comparison of two local anesthetic techniques for postoperative analgesia following day case circumcision. Acta Anaesthesiol Scand 1985;29:175–9.
11. Jensen BH. Caudal block for postoperative pain relief in children after genital operations: a comparison between bupivacaine and morphine. Acta Anaesthesiol Scand 1981; 25:373–5.
12. Kirya C, Werthmann MW Jr. Neonatal circumcision and penile dorsal nerve block—a painless procedure. J Pediatr 1978; 92:998–1000.
13. Broadman LM, Hannallah RS, Belman AB, Elder PT, Ruttimann U, Epstein BS. Post-circumcision analgesia—a prospective evaluation of subcutaneous ring block of the penis. Anesthesiology 1987;67:399–402.
14. Tree-Trakarn T, Pirayavaraporn S. Postoperative pain relief for circumcision in children: comparison among morphine, nerve block, and topical analgesia. Anesthesiology 1985;62:519–22.
15. Tree-Trakarn T, Pirayavaraporn S, Lertakyamanee J. Topical analgesia for relief of post-circumcision pain. Anesthesiology 1987;67:395–9.
16. Carlsson P, Svensson J. The duration of pain relief after penile block to boys undergoing circumcision. Acta Anaesthesiol Scand 1984;28:432–4.
17. Lau JTK. Penile block for pain relief after circumcision in children: a randomized, prospective trial. Am J Surg 1984; 147:797–9.
18. Sara CA, Lowry CJ. A complication of circumcision and dorsal nerve block of the penis. Anaesth Intensive Care 1984; 13:79–85.

ANESTH ANALG
1989;69:46–9

Incidence of Visceral Pain during Cesarean Section: The Effect of Varying Doses of Spinal Bupivacaine

Hilda Pedersen, MD, Alan C. Santos, MD, Ellen S. Steinberg, MD,
Howard M. Schapiro, MD, Terry W. Harmon, MD, and Mieczyslaw Finster, MD

PEDERSEN H, SANTOS AC, STEINBERG ES, SCHAPIRO HM, HARMON TW, FINSTER M. Incidence of visceral pain during cesarean section: the effect of varying doses of spinal bupivacaine. Anesth Analg 1989;69:46–9.

The safety of 0.5% hyperbaric bupivacaine, as well as the incidence and severity of visceral pain, were evaluated in 36 women undergoing elective cesarean section under spinal anesthesia who, randomly divided into two groups, received different dose ranges according to height, 7.5–10 mg in group A and 10–12.5 mg in group B. When sensory block to at least the fourth thoracic dermatome was established, surgery was begun and the occurrence and severity of visceral pain recorded (visual analog scale) by an observer unaware of patient data. The level of analgesia to pinprick was determined when and if there was onset of pain intraoperatively, and supplementary medication was administered as needed. Hypotension, the incidence of which was similar in both groups, was treated as necessary with ephedrine. No patients experienced pain until after delivery of the infant. Thereafter, moderate to severe pain, in association with peritoneal traction, occurred in 12 patients in group A (70.5%) but only in 6 patients in group B (31.6%). In patients experiencing moderate to severe pain, the mean time between induction of anesthesia and onset of pain was similar in both groups, as was the amount of systemic narcotic given. Total time for regression of sensory analgesia to L_5 *was longer in patients in group B (243.9 versus 195.4 min), and the incidence of complete motor blockade was greater in group B. Increasing the amount of 0.5% hyperbaric bupivacaine per spinal segment reduces the occurrence of moderate to severe visceral pain during elective cesarean section without jeopardizing mother or fetus.*

Key Words: ANESTHETICS, LOCAL—bupivacaine. ANESTHETIC TECHNIQUES—spinal. ANESTHESIA—obstetrical.

A recent survey of obstetric anesthesia practices in the United States revealed that 34% of patients having a cesarean section receive spinal anesthesia (1). Subarachnoid injection of lidocaine, tetracaine, or, more recently, bupivacaine, has been demonstrated to be safe and effective for this purpose. However, despite seemingly adequate levels of sensory block and regardless of the local anesthetic used, many mothers require supplemental analgesics to relieve pain associated with exteriorization of the uterus and traction on the abdominal viscera.

In our previous study, almost all mothers (19 of 22) given 0.5% hyperbaric bupivacaine (7.5–10 mg) for spinal anesthesia in cesarean sections required narcotic supplementation because of visceral pain (2). Hypotension occurred in only two patients. In another study, subarachnoid injection of larger doses, 11–15 mg, of 0.5% hyperbaric bupivacaine resulted in satisfactory analgesia for cesarean section, with only 4 of 33 patients requiring intraoperative narcotics (3). However, the risk of hypotension has led the authors to recommend that spinal anesthesia be limited to cases where there is no evidence of placental insufficiency. More recently, the quality of analgesia with the use of 12.5 mg of hyperbaric 0.5% bupivacaine was deemed excellent, although the incidence of maternal hypotension was 65% (4). The current study was undertaken to compare the safety of two dose ranges of 0.5% hyperbaric bupivacaine, as well as the incidence and severity of visceral pain, in patients having spinal anesthesia for cesarean section.

Received from the Department of Anesthesiology, Obstetrics and Gynecology, College of Physicians and Surgeons Columbia University, New York, New York. This study was presented in part at the Annual Meeting of the American Society of Regional Anesthesia, San Francisco, California, March 1988. Accepted for publication January 30, 1989.

Address correspondence to Dr. Pedersen, Department of Anesthesiology, Columbia-Presbyterian Medical Center, 622 West 168th Street, New York, NY 10032.

©1989 by the International Anesthesia Research Society

Methods and Materials

Healthy mothers (American Society of Anesthesiologists Class I or II) who chose to have spinal anesthesia for elective cesarean section were enrolled in the study, which was approved by the Institutional Review Board. Written informed consent was obtained at the preoperative visit. None of the patients had obstetric complications or evidence of fetal compromise. They received 15 mL of a sodium citrate solution orally and the rapid intravenous infusion of 1,500–2,000 mL of lactated Ringer's solution, as well as 50 mg of ephedrine by intramuscular injection, within 15 min before induction of spinal anesthesia.

Subarachnoid injection was performed in the sitting position at the L_{2-3} or L_{3-4} interspace with use of a 25 gauge spinal needle and a 19 gauge introducer. Mothers were randomly assigned to receive one of two dose ranges of 0.5% bupivacaine hydrochloride in 8.25% glucose monohydrate. Patients in group A were given 7.5–10 mg according to height, whereas those in group B received 10–12.5 mg of the drug. Group A mothers less than 158 cm tall were given 7.5–8.0 mg (1.5–1.6 mL), those between 160 and 170 cm received 8.5–9.0 mg (1.7–1.8 mL), whereas those taller than 170 cm received 10 mg (2.0 mL). In group B, the corresponding bupivacaine doses were 10–10.5 mg (2.0–2.1 mL); 11–11.5 mg (2.2–2.3 mL); and 12.5 mg (2.5 mL) respectively. After subarachnoid injection (over 30 sec), mothers were immediately placed in the supine 5–10° Trendelenburg position with left uterine displacement. The spread of sensory analgesia to pinprick was ascertained at 2-min intervals. If at 4 min, analgesia had not reached the eighth thoracic dermatome, the tilt was increased further to an approximately 20° head down position so as to extend the sensory block to the fourth thoracic segment. Patients in whom a T_4 level of pinprick anesthesia could not be achieved were excluded.

Motor function was also assessed at 2-min intervals with use of the Bromage scale (5) until draping of the surgical field: a score of 0 indicated no paralysis; 1, an inability to raise the extended leg; 2, inability to flex the knee; and 3, inability to flex the ankle joint.

After the desired level of anesthesia was established, another anesthesiologist, unaware of the amount of drug given, observed and recorded the occurrence and severity of visceral pain throughout the entire operation, as indicated by the patient on a 10-cm visual analog scale. A value of 3 or higher was considered to indicate moderate to severe pain. This anesthesiologist also recorded the level of analgesia to pinprick when and if visceral pain occurred and administered supplementary medication as needed.

Table 1. Demographic Characteristics

N	Group A (17)	Group B (19)
Age (yrs)	30.1 ± 1.2	31.6 ± 1.1
Height (cm)	159.6 ± 1.8	160.2 ± 1.5
Weight (kg)	78.2 ± 3.1	78.2 ± 3.1

Unpaired Student's *t*-test (differences not significant).

Maternal blood pressure measured by automated sphygmomanometry and heart rate by electrocardiograph were recorded every minute until delivery and every 5 min thereafter. If hypotension defined as systolic blood pressure below 100 mm Hg occurred, it was promptly treated by increasing both uterine displacement and the rate of intravenous fluid administration. If these measures were not successful, ephedrine 5–10 mg was injected intravenously and repeated as needed. Oxygen was administered routinely by face mask until delivery.

Induction-to-delivery and uterine incision-to-delivery intervals were recorded. The infant's Apgar score at 1, 2, and 5 min was assessed by an independent physician unaware of the mother's group assignment. At delivery, blood samples were taken from a doubly clamped segment of the umbilical cord for measurement of blood pH and gas tensions. All mothers received oxytocin by continuous infusion after delivery.

In the immediate postoperative period, the sensory level of analgesia and the degree of motor blockade were assessed at 15-min intervals until complete recovery from anesthesia.

Student's *t*-test for unpaired data, Fisher exact frequency analysis, and analysis of variance were used where appropriate ($P < 0.05$ was considered significant). All results are reported as mean ± SE.

Results

Thirty-eight patients were enrolled in the study, 19 in each group. Two patients in group A were excluded because the level of sensory analgesia at the fourth thoracic dermatome could not be achieved due to poor technique. In one, general endotracheal anesthesia was required, and in the other, incremental doses of ketamine.

Patients were similar insofar as age, height, and weight were concerned (Table 1). The mean dose of bupivacaine was significantly greater in group B, 10.89 ± 0.16 mg compared with 8.41 ± 0.16 mg in group A (Table 2). The dose per centimeter of height

Table 2. Mean ± SE Doses of Hyperbaric Bupivacaine

N	Group A (17)	Group B (19)
Dose (mg)	8.41 ± 0.16	10.89 ± 0.16*
Dose/height (mg/cm)	0.053 ± 0.001	0.068 ± 0.001*

*Unpaired Student's *t*-test ($P < 0.05$).

Table 3. Maternal Heart Rate and Systolic Blood Pressure Before 0 and up to 60 Min after Induction of Spinal Anesthesia (mean ± SE)

	Heart Rate (beats/min)		Systolic Blood Pressure (mm Hg)	
Group	A	B	A	B
Time (min)				
0	86.6 ± 2.9	86.2 ± 3.1	124.6 ± 3.8	121.6 ± 2.4
5	97.4 ± 3.8	95.5 ± 6.6	120.6 ± 3.5	121.3 ± 4.1
10	90.9 ± 3.7	90.5 ± 4.2	118.9 ± 2.1	114.8 ± 4.1
15	87.8 ± 3.1	84.3 ± 3.7	123.9 ± 2.6	119.8 ± 3.5
20	90.2 ± 2.5	87.1 ± 3.3	119.3 ± 2.2	118.1 ± 2.6
30	96.6 ± 2.9	89.3 ± 2.5	117.8 ± 3.1	114.1 ± 3.4
60	86.9 ± 3.8	85.4 ± 2.9	118.5 ± 3.1	118.5 ± 2.9

Analysis of Variance
Differences not significant.

was also greater in group B patients, 0.068 ± 0.001 mg/cm compared with 0.053 ± 0.001 mg/cm in group A ($P < 0.05$).

Although the highest level of sensory analgesia, T_1, occurred in 8 of 17 (47%) patients in group A and in 5 of 19 (26%) in group B, the difference was not statistically significant. Within the 10–15 min of preoperative testing, complete motor blockade (Bromage 3) was reached in 89% of group B patients compared with 47% of group A ($P < 0.05$). Total time for regression of sensory analgesia to L_5 was significantly longer in patients in group B than in those in group A, 243.9 ± 8.2 compared with 195.4 ± 6.7 min. In all patients, complete motor function had returned within 115 min of subarachnoid injection.

Mean maternal heart rate and systolic blood pressure after prehydration and administration of ephedrine, but before induction of spinal anesthesia, were 86.6 ± 2.9 beats/min and 124.6 ± 3.8 mm Hg, respectively, in mothers in group A, and in those in group B, 86.2 ± 3.1 beats/min and 121.6 ± 2.4 mm Hg (Table 3). In general, these were well maintained, and no differences between groups were detected at 5, 10, 15, 20, 30, and 60 min after spinal injection. Four of 17 (24%) patients in group A developed transient hypotension soon after induction, and 3 of them required intravenous injection of ephedrine (5–10 mg) when conservative measures had failed to restore normotension. Hypotension occurred in 5 of 19 (26%) mothers in group B also before surgery, each of the 5 requiring intravenous administration of ephedrine. There were no significant differences between groups in the incidence of hypotension or need for ephedrine.

The mean interval from induction of anesthesia to delivery was 20.8 ± 1.6 min and 20.0 ± 1.2 min in mothers in group A and B, respectively. The interval between uterine incision and delivery was less than 180 seconds in all cases.

The mean gestational age and weight of infants in both groups were similar. In group A, these were 39.1 ± 0.3 weeks and 3447 ± 82.7 g, respectively, and 39.2 ± 0.3 weeks and 3326 ± 89.4 g, respectively, for infants in group B. Neonatal condition was good. One infant in group B had a 1 min Apgar score of 5; no infant had an Apgar score less than 8 at 5 min. Umbilical arterial and venous blood samples, obtained from all infants except one in group A, showed blood pH and gas tensions to be similar in both groups (Table 4).

No mother complained of visceral pain before delivery of the infant. After delivery, moderate to severe pain occurred in 12 (70.5%) patients in group A but in only 6 (31.6%) patients in group B in association with peritoneal traction (exteriorization of the uterus and closure of the peritoneum). The difference between the two groups was statistically significant. The mean time between induction of spinal anesthesia and onset of pain was 34.4 ± 4.0 min in group A, which was similar to that observed in group B patients, 41.0 ± 4.8 min, at which time the sensory level of analgesia was T_4 or higher in all except one patient in group A. The mean duration of surgery was also similar in both groups; 66.5 ± 6.2 min in group A and 67.9 ± 4.6 min in group B. All patients reporting moderate to severe pain received supplementary intravenous medication. The amount of systemic analgesia given in morphine equivalents (1 mg morphine = 10 mg meperidine), was similar, namely 7.96 ± 1.2 mg in group A and 7.92 ± 1.1 mg in group B. One patient in group B received ketamine 10 mg; diazepam 5 mg was given to two patients in group A. Droperidol 1.25 mg was given to 11 patients in group A and 13 in group B. It was administered after delivery either prophylactically along with narcotic pain medication (five patients in group A, seven in group B), or for treatment of nausea that occurred in association with moderate to severe pain (two in group A, three in group B), or as the only symptom (four in group A, three in group B).

Discussion

Our data indicate that subarachnoid injection of 0.5% hyperbaric bupivacaine is safe and effective in estab-

Table 4. Blood pH and Gas Tensions in Umbilical Artery and Vein (mean ± SE)

	pH		PCO_2 (mm Hg)		PO_2 (mm Hg)	
	UV	UA	UV	UA	UV	UA
Group A (N = 16)	7.31 ± 0.01	7.22 ± 0.01	37.9 ± 1.2	50.5 ± 2.3	33.7 ± 1.5	17.3 ± 1.3
Group B (N = 19)	7.33 ± 0.01	7.24 ± 0.01	35.1 ± 1.2	43.9 ± 2.8	32.6 ± 1.6	14.9 ± 0.8

Unpaired Student's *t*-test (differences not significant).

lishing anesthesia for cesarean section. The group of patients given approximately 25% higher dose of drug per centimeter of height had a reduced occurrence of moderate to severe visceral pain without compromise of maternal and fetal well being. Administration of a higher dose of drug, however, did lead to a slower regression of sensory analgesia and a greater incidence of complete motor blockade of the lower extremities (Bromage 3). Other studies (2,4,6) also indicate that with the use of 0.5% hyperbaric bupivacaine for spinal anesthesia, increasing the dose increases the duration of sensory and the profundity of motor blockade. There was no significant difference in the frequency of sensory analgesia extending to T_1 between groups. This lack of difference may be explained by the recent observation that the spread of a hyperbaric local anesthetic solution after subarachnoid injection does not correlate with the mother's height, weight, or body mass index (7).

Transient hypotension, soon after induction of anesthesia, occurred with similar frequency in both groups and was readily corrected with additional hydration and, in most cases, with the administration of a small intravenous dose of ephedrine. The incidence of hypotension in our patients given 7.5–10 mg bupivacaine (24%) was greater than the 9% previously reported by us (2). The latter study included a significant number of patients in labor. The tendency for hypotension to develop after regional anesthesia is less in laboring mothers undergoing cesarean section than it is in those having elective sections (8).

Neonatal condition assessed by Apgar score and umbilical blood pH and gas tensions was good in both groups. One infant in group B had an Apgar score of 5 at 1 min. However, the score at 2 min was 9, and the umbilical cord blood pH and gas tensions were normal, namely pH 7.28, PCO_2 45 mm Hg and PO_2 49 mm Hg in the umbilical vein, and pH 7.22, PCO_2 69 mm Hg and PO_2 18 mm Hg in the umbilical artery.

It is generally accepted that sensory analgesia to at least the fourth thoracic dermatome is necessary for cesarean section. However, even with this extent of block a substantial proportion of patients require supplementary analgesia during exteriorization of the uterus and traction on the abdominal viscera (9). All patients retained in this study had a similar spread of sensory block to above the T_4 level, yet the use of higher doses of bupivacaine resulted in a lesser frequency of moderate to severe visceral pain. Visceral pain, like tourniquet pain, is believed to be transmitted by unmyelinated C fibers. It has recently been postulated that with declining concentrations of local anesthetic in the cerebrospinal fluid, these fibers may become unblocked, although the conduction in A-delta fibers transmitting incisional pain has not been restored (10). Because in our patients occurrence of pain could not be attributed to regression of sensory analgesia, it appears that an increase in the amount of drug per spinal segment improves the overall quality of blockade.

References

1. Gibbs CP, Krischer J, Peckham BM, Sharp H, Kirschbaum TH. Obstetric anesthesia: a national survey. Anesthesiology 1986; 65:298–306.
2. Santos A, Pedersen H, Finster M, Edström H. Hyperbaric bupivacaine for spinal anesthesia for cesarean section. Anesth Analg 1984;63:1009–13.
3. Willdeck-Lund G, Lyrenas S, Edström H. Spinal anaesthesia for caesarean section (abstr). Acta Anaesthesiol Scand 1983; 78(suppl):98.
4. Michie AR, Freeman RM, Dutton DA, Howie HB. Subarachnoid anaesthesia for elective Caesarean section. A comparison of two hyperbaric solutions. Anaesthesia 1988;43:96–9.
5. Bromage PR, Burfoot MF, Crowell DE, Pettigrew RT. Quality of epidural blockade. I. Influence of physical factors. Br J Anaesth 1964;36:342–52.
6. Chambers WA, Littlewood DG, Edström HH, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume administered. Br J Anaesth 1982;54:75–80.
7. Norris MC. Height, weight and the spread of subarachnoid hyperbaric bupivacaine in the term parturient. Anesth Analg 1988;67:555–8.
8. Brizgys RV, Dailey PA, Shnider SM, Kotelko DM, Levinson G. The incidence and neonatal effects of maternal hypotension during epidural anesthesia for cesarean section. Anesthesiology 1987;67:782–6.
9. Brownridge P, Jefferson J. Central neural blockade and caesarean section II: patient assessment of the procedure. Anaesth Intensive Care 1979;7:163–8.
10. Concepcion MA, Lambert DH, Welch KA, Covino BG. Tourniquet pain during spinal anesthesia: a comparison of plain solutions of tetracaine and bupivacaine. Anesth Analg 1988; 67:828–32.

ANESTH ANALG
1989;69:50–2

Prolonged Nasotracheal Intubation and Its Association with Inflammation of Paranasal Sinuses

Argyro Fassoulaki, MD, PhD, DEAA, and Philippos Pamouktsoglou, MD

FASSOULAKI A, PAMOUKTSOGLOU P. Prolonged nasotracheal intubation and its association with inflammation of paranasal sinuses. Anesth Analg 1989;69:50–2.

Sixteen critically ill patients whose tracheas were intubated through the nasal route were examined for paranasal sinusitis between the 2nd and 3rd day and again on the 8th day after intubation. Between the 2nd and 3rd days, 6 of the 16 patients developed either maxillary sinusitis alone (3 of them) or sphenoid sinusitis (in the other 3). By the 8th day, all patients had developed sinusitis involving at least one sinus. The most commonly affected sinuses were the maxillary (87%) and the sphenoid (87%) followed by the ethmoid (50%) and frontal (12.5%). On the day 8 after intubation, the nasotracheal tubes were removed and replaced by orotracheal tubes, or tracheostomies were performed. On day 8 after extubation, 10 of the 16 patients were reexamined. Computer tomographic (CT) scan at this time revealed persistent sinusitis in two. Long-term nasotracheal intubation is associated with sinusitis.

Key Words: INTUBATION, TRACHEAL—nasal. INFECTION—sinusitis. COMPLICATIONS—sinusitis.

Early tracheostomy for airway management in critically ill patients has been superseded by prolonged tracheal intubation. The nasal route for prolonged intubation of the trachea is generally preferable to the oral route as the tube is better tolerated by the patient and allows easier access for the toilet of the oral cavity. However, as prolonged intubation of the trachea becomes more widely used, more complications associated with it are becoming recognized. This prospective study investigates the incidence and the time of onset of paranasal sinusitis during prolonged nasotracheal intubation as determined by means of computerized scanning techniques.

Methods

Sixteen patients admitted to the intensive care unit (ICU) requiring ventilation of the trachea and mechanical support of ventilation were studied. The study was approved by the local ethical committee. Reasons for admission to the ICU included postoperative respiratory failure (5), coma due to poisoning with sedatives and narcotics (3), respiratory failure due to near drowning (2), Guillain-Barré syndrome (2), and one each for exacerbation of preexisting chronic respiratory failure and for tetanus. Two of the 16 patients were admitted because of trauma (but without head injury or fractures of the facial bones). Ages varied between 21 and 75 years with a mean ± SD of 46 ± 16.5 years. In all cases, emergency intubation was performed through the oral route; nasogastric tubes were inserted through the oral route as well.

Patients were mechanically ventilated with an Engström Erica ventilator. $\dot{V}O_2$ and $\dot{V}CO_2$ were continuously measured by means of an Engström Metabolic Computer and an infrared carbon dioxide analyzer (Engström-Eliza), as described in previous studies (1,2). Criteria to enter the study included absence of preexisting sinusitis and evidence of sepsis (for example, hyperpyrexia, high $\dot{V}O_2$ and $\dot{V}CO_2$) and negative nitrogen balance. All patients underwent examination (computer tomographic [CT] scan) of the paranasal sinuses to exclude preexisting sinusitis, after which the oral tubes were replaced by nasal tubes. All nasotracheal tubes were size 7.5 or 8 mm internal diameter, ethylene oxide sterilized, soft cuff polyethylene tubes. CT scan was repeated in each patient between the 2nd and 3rd and on the 8th day after intubation. On day 8, the nasal tube was re-

---

Received from the Department of Intensive Care Unit, St. Savas Hospital, University of Athens, Medical School, Athens, Greece. Accepted for publication on January 31, 1989.

Address correspondence to Dr. Fassoulaki, 57-59 Raftopoulou Street, Athens 11744, Greece.

©1989 by the International Anesthesia Research Society

Table 1. Sinusitis Development in the 16 Patients with Nasal Intubation of the Trachea and Course of Resolution in 10 of the 16 Patients

Type of Sinusitis	Before Intubation	Days 2–3 after Intubation	Day 8 after Intubation	8 Days after Removal of the Tube
Maxillary	0/16 (0%)	3/16 (19%)	14/16 (87%)	1/10 (10%)
Sphenoid	0/16 (0%)	3/16 (19%)	14/16 (87%)	1/10 (10%)
Frontal	0/16 (0%)	0/16 (0%)	2/16 (12.5%)	1/10 (10%)
Ethmoid	0/16 (0%)	0/16 (0%)	8/16 (50%)	0/10 (0%)

moved and either replaced by an oral tube, or a tracheostomy was performed.

Soon after day 8, and when paranasal sinusitis was diagnosed, three patients died and three were extubated and discharged from the unit. In the remaining 10 patients, the course of paranasal sinusitis was examined with CT scan 8 days after the removal of the nasotracheal tube. The CT scans were assessed for thickening of the mucosa, air-fluid levels, and opacification. The term sinusitis does not necessarily imply infection (3). No bacteriological specimens were obtained as ear, nose, and throat surgeons and the ethical committee objected to antral puncture in these patients for study purposes. To obtain specimens from other sinuses such as the sphenoid sinus was out of the question.

At the time of the study, all patients were being treated with antibiotics. Patients on admission who were comatose due to overdosage or near drowning and who had inhaled gastric contents were given cephalosporin type antibiotics. The surgical or trauma cases had an aminoglycoside combined with an antianaerobic agent.

Results

Between days 2 and 3 after intubation, 3 of the 16 patients developed maxillary sinusitis and 3 developed sphenoid sinusitis. By day 8, when the CT scan was repeated, all 14 of the 16 patients had developed sinusitis involving more than one sinus and 2 had sinusitis of the sphenoid sinus alone (Table 1). Fluid accumulation was diagnosed with CT scan in all cases. Sinusitis, though involving different and more than one sinuses, was unilateral in all instances and on the same side as the tracheal tube.

CT scan on day 8 revealed sphenoid sinusitis in 14 (87%) and maxillary sinusitis in 14 (87%) of the 16 patients studied. At the same time, the ethmoid sinus was involved in eight patients (50%), whereas two patients (12.5%) had frontal sinusitis. As far as the radiographic findings are concerned, an air-fluid level was detected in all but two of the affected sinuses and in these two, opacification was observed. Clearing of the sinuses by CT scan was seen in 8 of the 10 patients available for CT scan 8 days after removal of the nasotracheal tube, who in the meantime had had a tracheostomy performed or an orotracheal tube inserted. In two patients, resolution of the sinusitis, though started, was not complete. In one patient, air-fluid levels in the maxillary and frontal sinuses were detected, whereas the second patient still had sphenoid sinusitis.

Discussion

In the 16 patients we studied, the nasotracheal tube blocked sinus drainage through the nasal ostia, resulting in unilateral sinusitis involving different sinuses, in all instances on the same side of the endotracheal tube. Sinusitis was documented on CT scan with no signs of mucopurulent drainage around the nasotracheal tube or evidence of sepsis. Headache, facial pain, paresthesia of the opthalmic or maxillary dermatomes of the fifth nerve, or purulent nasal discharge was not or could not be observed in these intubated patients.

Deutschman et al. (4) reported 27 cases of paranasal sinusitis as a consequence of nasotracheal intubation in a surgical and trauma unit over a 2-year period. These investigators proceeded to radiological examination only after clinical evidence of sinusitis developed, such as mucopurulent drainage around the tube or sepsis of unrecognized source.

Our study demonstrates that a nasotracheal tube left in place for as long as 8 days results in fluid accumulation in one, but usually more than one, sinus. As no bacteriological specimens were obtained, the sinusitis diagnosed by CT scan is not necessarily associated with bacterial infection. However, nasotracheal intubation and air-fluid levels in the sinuses predispose head injured patients to bacterial sinusitis and meningitis (5).

The time needed to detect sinusitis in all our patients was longer than 2 or 3 days. The time of onset of symptomatic sinusitis associated with nasotracheal intubation has been said to differ with emergency and elective intubation (4). Our policy is to intubate the trachea through the nasal route electively, whereas in the emergency situation, we use the oral route. We consider the latter safer because the oral route is less time consuming and the danger of nasal bleeding is avoided. The diagnostic accuracy of sinusitis with standard film radiography is low (6).

CALCU

In a previous study (7), conventional lateral and submental lateral views failed to demonstrate sphenoid sinus infection in several patients. On the contrary, computerized axial tomography is a reliable radiographic examination for diagnosis of sphenoid sinusitis (8). A number of case reports of paranasal sinusitis due to nasotracheal intubation are based on x-ray films and not on CT scan (9–11). This finding may explain why maxillary but not sphenoid sinusitis was detected in these cases.

It has been reported (4) that the clinical symptoms of paranasal sinusitis associated with nasotracheal tubes disappear within 48 hrs after removal of the nasotracheal tube. Nevertheless, in two of our patients, sinusitis was diagnosed by CT scan 8 days after the removal of the tube. As infection and sepsis in the critically ill patient are multifactorial, a coexisting source of infection may escape the attention or even the diagnosis of the intensivist.

In a study (12) investigating the incidence of sinusitis associated with nasotracheal intubation, neither the incidence of individual sinus involvement nor the course of resolution of sinusitis was considered. Of the 12 patients in that study, 6 had cranial trauma. However, penetrating craniocerebral injury and bleeding into sinuses render the CT scan positive for sinusitis. This correlation probably explains the finding that 100% of patients in that study had CT scan evidence of sinusitis 1 or 2 days after nasotracheal intubation. The association of nasotracheal intubation and sinusitis needs to be studied in patients without head injury.

In conclusion, prolonged nasotracheal intubation is associated with fluid accumulation involving one or more paranasal sinuses. Such fluid accumulation may well be an indicator of impending or potential paranasal sinusitis.

References

1. Fassoulaki A, Eforakopoulou M, Vassiliou M. Metabolic responses—($\dot{V}O_2$, $\dot{V}CO_2$ and energy expenditure)—associated with nasal intubation of the trachea. Anesth Analg 1989; 68:112–5.
2. Fassoulaki A, Eforakopoulou M. Cardiovascular, respiratory and metabolic changes produced by pressure supported ventilation in ICU patients. Crit Care Med 1989 (in press).
3. Thomson DR, Sherman SR. Nosocomial infections in traumatized patients-Sinusitis. In: Farber BF, ed. Infection Control in Intensive Care. New York: Churchill Livingstone, 1987:109–10.
4. Deutschman CS, Wilton P, Sinow J, Dibbell D, Konstantinides FN, Cera FB. Paranasal sinusitis associated with nasotracheal intubation: a frequently unrecognized and treatable source of sepsis. Crit Care Med 1986;14:111–4.
5. Grindlinger GA, Niehoff J, Hughes SL, Humphrey MA, Simpson G. Acute paranasal sinusitis related to nasotracheal intubation of head injured patients. Crit Care Med 1987;15:214–7.
6. Chidekel N, Jensen C, Axelsson A, Grebelius N. Diagnosis of fluid in the maxillary sinus. Acta Radiol [Diagn] (Stockh) 1970;10:433–40.
7. Lew D, Southwick FS, Montgomery WW, Weber AL, Baker AS. Sphenoid sinusitis. N Engl J Med 1983;309:1149–54.
8. Forbes WStC, Fawcitt RA, Isherwood I, Webb R, Farington T. Computed tomography in the diagnosis of diseases of the paranasal sinuses. Clin Radiol 1978;29:501–11.
9. Knodel AR, Beekman JF. Unexplained fevers in patients with nasotracheal intubation. JAMA 1982;248:868–70.
10. Arens JF, LeJeune FE, Werbe DR. Maxillary sinusitis, a complication of nasotracheal intubation. Anesthesiology 1974; 40:415–6.
11. Gallager TJ, Civetta JM. Acute maxillary sinusitis complicating nasotracheal intubation. A case report. Anesth Analg 1976; 55:885–6.
12. Hansen M, Poulsen MR, Bendixen DK, Hartmann-Andersen F. The incidence of sinusitis in patients with nasotracheal intubation. Br J Anaesth 1988;61:231–2.

Interaction of Lidocaine and Hypothermia in Bier Blocks in Volunteers

James E. Heavner, DVM, PhD,* Lea Leinonen, MD, PhD, Juhani Haasio, MD, Juha Kytta, MD, and Per H. Rosenberg, MD, PhD

HEAVNER JE, LEINONEN L, HAASIO J, KYTTA J, ROSENBERG PH. Interaction of lidocaine and hypothermia in Bier blocks in volunteers. Anesth Analg 1989;69:53–9.

The present investigation was designed to study the interaction of temperature, lidocaine, and ischemia during intravenous regional anesthesia (IVRA) of the arm. Five volunteers were studied during exposure of one of their arms to four different experimental conditions: hypothermia and ischemia; hypothermia, ischemia, and lidocaine; normothermia and ischemia; normothermia, ischemia, and lidocaine. Each subject was tested on four different occasions with only one test condition imposed per occasion and with 3 or more days between experiments. Somatosensory evoked responses (SERs) and muscle responses to ulnar nerve stimulation were measured, and sensory testing was done to determine whether the neural effects of the particular treatments differed. Anesthesia developed sooner and was more extensive when local anesthetic was injected. A 5–10°C decrease in tissue temperature did not accentuate the anesthetic effects of lidocaine as determined by time to loss of pinprick and touch sensation. With ischemia alone, anesthesia of the finger tips with preservation of sensation on the arm was observed in all subjects 20 min after tourniquet inflation. Anesthesia at all cutaneous test sites was achieved in 7 of 10 lidocaine experiments; no systematic order of sensory loss, such as progression from distal to proximal sites, was observed. Decrease in limb temperature slowed the development of lidocaine effects on evoked responses and recovery from the effect. Under conditions of ischemia, deterioration of sensation generally began earlier under cold rather than warm conditions. Primary differences between changes in the SERs and muscle responses under condition of ischemia versus ischemia and lidocaine were the rate and magnitude of change of potential latency and amplitude. Venous lidocaine plasma levels were similar after tourniquet release with normothermia and hypothermia. Based on in vitro experiments, the expectation that cooling the arm would decrease time to onset of anesthesia and enhance the intensity and extent of the block was not met.

Key Words: NERVE—evoked potentials. TEMPERATURE—hypothermia. ANESTHETIC TECHNIQUES, INTRAVENOUS REGIONAL—Bier block. ANESTHETICS, LOCAL—lidocaine.

The conduction blocking effect of local anesthetics on isolated nerves is potentiated by cold temperature. For instance, Franz and Perry (1) found that cooling by 5–10°C increases the nerve-blocking effect of procaine. We demonstrated that cold temperature potentiates the effect of lidocaine on isolated nerves (2). Depending on the type of nerve fiber and animal species, conduction in mammalian peripheral nerves is completely blocked at temperatures below 20°C (usually around 10°C) (3,4).

Therefore, cooling of the extremity might reduce the time to onset of anesthesia and enhance the quality of analgesia provided by intravenous regional anesthesia (IVRA, Bier block). The present investigation was designed to study the interaction of temperature, lidocaine, and ischemia during IVRA of the arm.

Methods

Five healthy male anesthesiologists, 33–42 years of age, participated in the study. Informed consent was

---

Received from the *Department of Anesthesiology and Physiology, Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas and the Department of Neurosurgery and Anesthesiology, Helsinki University Central Hospital, Helsinki, Finland. Accepted for publication January 30, 1989.

Supported by a Fulbright Award, Council for the International Exchange of Scholars, Washington, DC, and an award from The American-Scandinavian Foundation, New York, NY, and The Sigrid Juselius Foundation, Helsinki, Finland, and conducted at Toolo Hospital, Helsinki, Finland.

This study was presented in part at the Fifth World Congress on Pain, Hamburg, West Germany, August 1987 and the Ninth World Congress of Anesthesiologists, May 1988, Washington, DC.

Address correspondence to Dr. Heavner, Anesthesiology, Texas Tech University Health Sciences Center, Lubbock, TX 79430.

©1989 by the International Anesthesia Research Society

obtained before the experiments. Each subject was given four treatments in random fashion, each of which was separated by no less than a 3-day interval: exsanguination of nondominant (always left) arm and application of tourniquet during normothermia and hypothermia without and with intravenous lidocaine administration.

The arm was exsanguinated by elevating it and compressing the brachial artery for 2 min. A 8.5-cm wide tourniquet around the upper arm was then inflated to 275–300 mm Hg for 22–23 min. In the lidocaine experiments, 3 mg/kg of normal body weight (0.6 mL/kg) of a 0.5% solution was injected at a rate of 20 mL/min into a vein on the dorsum of the hand immediately after tourniquet inflation. Seven venous blood samples were drawn for lidocaine assay (5) through a cannula in a cubital vein of the right arm: before lidocaine administration, immediately before cuff deflation, and 2, 5, 10, 20, and 30 min after cuff deflation.

Arterial blood pressure was measured with use of an oscillotonometer every 5 min during the experiments. During the lidocaine experiments, electrocardiograph (ECG) was also monitored. No changes in blood pressure or heart rate exceeding 30% of baseline levels were observed during the experiments.

Skin temperature of the left arm was adjusted to 33°C or 22°C with cold/hot packs (Riker 3M) cooled to −2–5°C or warmed to 90°C. A towel was placed between the skin and the 90°C pack to prevent burning. The warming or cooling was started 10–15 min before tourniquet inflation and continued throughout the experiment. During experiments with hypothermia, the arm was rewarmed to 33°C starting 30 min after tourniquet deflation. Skin temperature was measured with a digital thermometer at the volar surface of the third finger tip, at the wrist, and at the forearm just distal to the elbow. Two of the subjects participated in separate experiments in which deep muscular temperatures ("moving muscle" thermoprobe) were monitored under similar conditions. In a normothermic arm, tissue temperatures at the depth of 2–3 cm remained stable and close to skin temperature (33°C). Cooling decreased the temperature to 31.5°C before tourniquet inflation and to 26.5°C during the 20-min ischemia. We also estimated temperature of the nerve using the following assumptions: linear decrease of temperature during the ischemic phase, decrease in nerve conduction velocity at a rate of 2.0 m/sec/C° (6) [for example, 70 m/sec (initial conduction velocity) − 50 m/sec (conduction velocity after cooling) = 10/2 = 5°C temperature change; initial temperature = 33°C − 5C = 28°C (final temperature)].

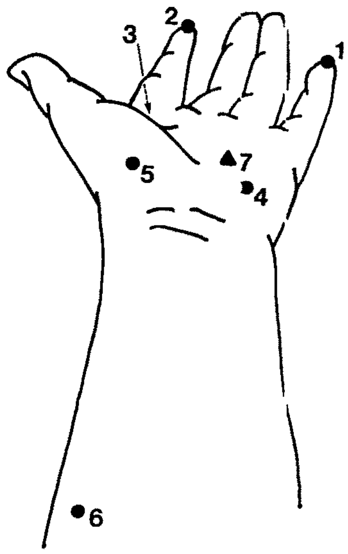


Figure 1. The hand figure shows the test sites: 1 and 4 = ulnar; 2 and 3 = median innervation areas at the palmar side of the hand; 5 = radial innervation area on the dorsum of the hand; 6 = musculocutaneous innervation area on the arm; and 7 = site of electrical stimulation of the median nerve sensory branches.

Sensory Measurements

Sensitivity to pinprick and blunt touch (tip and hub, respectively, of a 21-gauge needle) was measured at six locations shown in Figure 1. Sensations evoked by electric stimulation at the palm, used in the neurophysiological measurements, were also documented.

Neurophysiological Measurements

Responses to electrical stimulation of the sensory branches of the median nerve at the palm were recorded on four channels with a Sensor recorder (Medelec). The stimulation (3 Hz) was given through two stainless steel wire electrodes inserted subdermally along the course of the I and III common palmar digital nerves. The strength of the 0.3-ms stimulus was adjusted to produce painless sensation radiating into the second, third, and fourth finger (6–12 mA). In one experiment, the stimulus also radiated to the fourth and fifth finger. Compound action potentials 1) of the median nerve were recorded with two surface plate electrodes 2–3 cm apart about 19 cm distally to the cuff; 2) of the brachial plexus responses were recorded with two surface electrodes, one at Erb's point and the other 4–5 cm proximally; 3) of the medulla and lower brain stem were recorded with two surface electrodes, one over the seventh cervical spinal process and the other at Fpz[1]; and 4) of early cortical responses were recorded with needle electrodes at C4′[1] (2 cm posterior to C4[1]) and Fz[1]. A total of 128 responses were averaged with use of a 50-msec analysis time and 1 Hz–3 kHz bandpass for all channels. Automatic artifact rejection (at amplitude levels exceeding 5–10 times the signal) was used in all measurements; the number of stimulations for a single average varied from 140 to 200. Outputs were immediately printed. The signals from Sensor's analog output unit were stored on tape with a Racal 8-channel FM-recorder for off-line analysis of late somatosensory responses from C4'[1]-Fz. These analyses were made by averaging 120–180 responses by computer (Micro PDP Digital Equipment Co.) with use of a 200-msec analysis period and 1.3-kHz sampling rate.

Hypothenar muscle responses to transcutaneous ulnar nerve stimulation (0.2-msec supramaximal rectangular pulses) at the elbow were recorded with two surface plate electrodes or two subcutaneous wire electrodes with Medelec's electromyography (EMG) equipment. Signals obtained from the electrodes over the hypothenar muscle of three subjects during slight isometric adduction of the fifth finger were recorded (bandpass 8–800 Hz) intermittently on tape in seven experiments. Subsequently, power spectra of 10 consecutive 1-sec samples were analyzed off-line with the Micro PDP Computer.

Sensory measurements and evoked responses were recorded before tourniquet inflation, 2.5, 5, 7.5, 10, 15, and 20 min after tourniquet inflation, and 2.5, 5, 7.5, 10, 20, 30, 45, and 60 min after deflation.

Data comparisons were made by multivariant analysis (ANOVA) and the two-tailed *t*-test for paired data. Evoke response latencies, amplitudes, and durations were normalized to facilitate comparison of results obtained under different experimental conditions (100% is the normalized control value in each experiment).

Results

There were no differences between the anesthetic effects under warm and under cold conditions. Anesthesia developed sooner and was more extensive when local anesthetic was injected.

Measures of deep muscle temperature and estimates of nerve temperature indicate that temperature within the arm under conditions of hypothermia fell to about 24–26°C. Figure 2 shows median nerve sensory conduction velocities between the palm and cubita during normothermia and hypothermia and the range of neural temperatures estimated from conduction velocity changes as described in Methods. Lowest estimated temperatures were about 24°C 20 min after tourniquet inflation. After tourniquet release, tissue temperatures remained low. Rewarming for 20–30 min did not return conduction velocities quite back to baseline values.

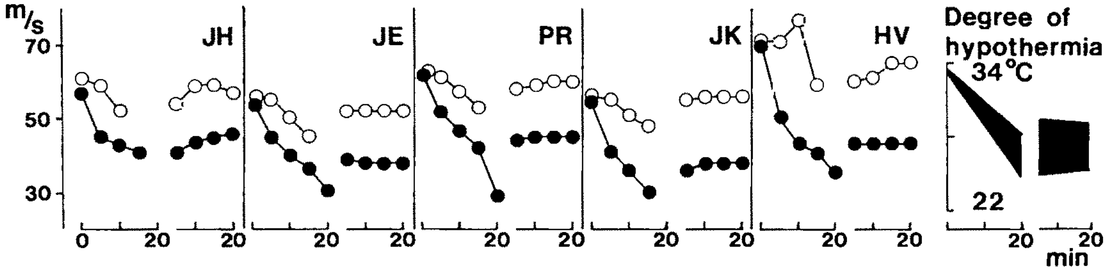


Figure 2. Median nerve conduction velocities during tourniquet inflation (0–20 min) and after deflation (2.5–20 min) under normothermic (**open symbols**) and hypothermic (**closed symbols**) conditions for all five subjects. The graph on the right shows the estimated range of nerve temperatures in the hypothermia studies.

Lidocaine Effects

Anesthesia at all cutaneous test sites was achieved in 7 of 10 lidocaine experiments; some sensation was preserved in three cases in the distribution of the musculocutaneous nerve. Pinprick and touch sensation was lost 2.5–15 min after lidocaine injection. The pattern and time course of sensory changes were similar during warm and cold conditions. In 31 out of 58 test sites, pinprick sensation was lost before blunt touch; both were lost simultaneously in the other sites. At the sites that became anesthetic, the fastest onset was in the areas innervated by the musculocutaneous and radial nerves. No systematic order of sensory loss, such as progression from distal to proximal sites, was observed. Cutaneous sensation recovered within 2.5 min after tourniquet deflation at 17 of 30 test sites; recovery times of 10–30 min were observed only at four test sites. In 8 of 10 lidocaine experiments, the electrical stimuli at the palm were not perceived at 20 min.

---

[1] International 10–20 System for Electroencephalography.

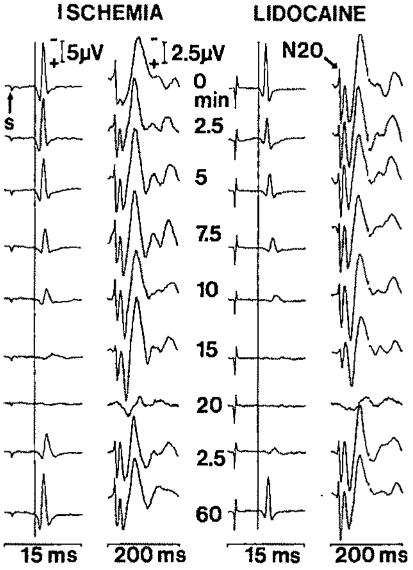


Figure 3. Median nerve compound action potentials and cortical responses to electrical stimulation of the palmar branches of the median nerve in one subject under normothermic conditions with and without lidocaine. S = stimulus artifact. N2O = first cortical amplitude. Potentials are arranged in order obtained with control at top and recovery at bottom.

Ischemic Effects

The effects of ischemia alone on pinprick and touch sensation appeared within 15–20 min. At 20 min, anesthesia of the fingertips with preservation of sensation on the arm was observed in all subjects. Deterioration of sensation (loss of pinprick sensation) generally began earlier under cold than under warm conditions and was not always corrected by restoration of circulation. It is possible that cooling of receptive skin areas under the cold packs caused this deterioration. Out of 42 test sites where some sensory loss occurred, pinprick sensation disappeared first in 20 and blunt touch in 5. Anesthesia to electrical stimulation of the median nerve at the palm developed in only two experiments. The quality of stimulus perception, however, changed considerably. Distal extent of radiating sensation diminished; the stimulus was felt as local and burning or painful.

Sensory Responses Evoked by Median Nerve Stimulations

Median nerve stimulations. Figure 3 shows simultaneous recordings of median nerve compound action potentials distal to the tourniquet and cortical evoked responses during normothermia in one subject. Compound action potential latencies increased, amplitudes decreased, and durations increased more rapidly after lidocaine injection than during ischemia alone. In both instances (ischemia alone and ischemia plus lidocaine), amplitude of the first cortical response, N2O, was markedly decreased when the compound action potential was near the detection threshold at 15 min. After disappearance of the median nerve potential at 20 min, a 50–150 msec cortical response was still detected in both experiments. After 20 min of ischemia, the subject still perceived the electric stimulation, whereas in the lidocaine experiment, the stimulus site was anesthetic. During ischemia, cortical responses after the N2O potential increased as N2O decreased, whereas after lidocaine all cortical responses decreased simultaneously. Similar changes were observed in one other subject; in three subjects with responses of smaller amplitudes and more complex patterns, there were no clear differences between the pattern of response changes in the two situations.

Figure 4 summarizes the changes in responses distal to the tourniquet after median and ulnar nerve stimulation during the four different conditions. Characteristics of baseline (33°C) median nerve responses recorded at the elbow after stimulation at the palm are shown in Table 1.

Significant ($P < 0.02$) increases in latency were present within 7.5 min during normothermic ischemia; lidocaine effects were clear at 5 min ($P < 0.01$; Figure 4A). Recovery of latencies was significantly slower after lidocaine treatment than without it. Ischemic effects disappeared in 7.5 min, but lidocaine effects were still present at 20 ($P < 0.01$) as well as at 60 min ($P < 0.001$).

Median nerve sensory potential amplitudes (Figure 4B) decreased and durations (Figure 4C) increased significantly after 7.5 min of normothermic ischemia ($P < 0.001$) and 2.5 min after lidocaine injection ($P < 0.001$). At 15 and 20 min, responses could be recorded in 1 of 10 attempts after lidocaine injection under normothermic conditions and in 6 of 10 recordings under hypothermic conditions. The recovery of potential amplitudes after ischemia took place within 10 min. In lidocaine experiments, amplitudes failed to recover in 20 min or even within 60 min after tourniquet release.

The amplitudes were smaller and durations longer 15–20 min after tourniquet release in the lidocaine/hypothermia experiments as compared with lidocaine/normothermia experiments. The differences could not be accounted for by hypothermia alone.

Motor Responses on Ulnar Nerve Stimulation

Latencies of hypothenar muscle responses to ulnar nerve stimulation at the elbow were between 6.2 and

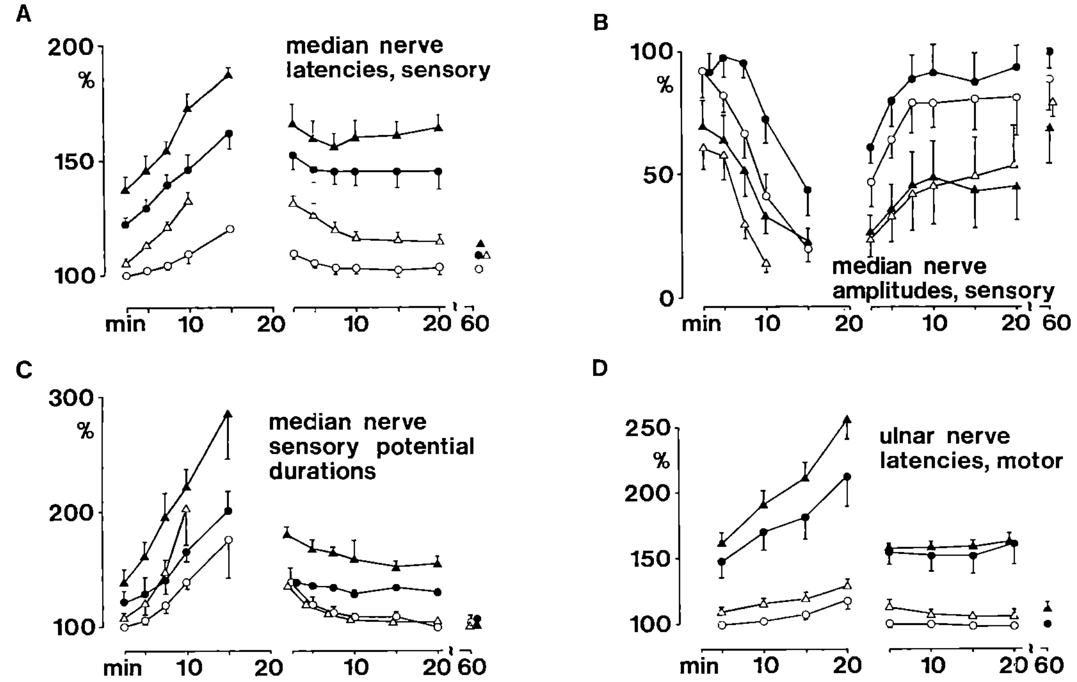


Figure 4. Average changes (percent of control ± SEM) in compound action potential (sensory) responses of the median nerve (A–C) and motor responses of the ulnar nerve (D) under the four different conditions. Circles = ischemia; triangles = ischemia with lidocaine; open symbols = warm; closed symbols = cold.

Table 1. Median Nerve Response Characteristics (33°C)*

Latency†	Amplitude‡	Duration§
4.0–6.1 ms (5.3 ± 0.7)	1.7–50 μV (12 ± 10.6)	1.4–3.0 ms (1.8 ± 0.6)

*Range (mean ± SD);
†To the beginning of the negative potential;
‡From beginning of the negative potential to the peak;
§Of the negative peak.

10.6 ms (X = 7.4 ± 1.0 ms). They were prolonged in four subjects at 15 min and in all five subjects at 20 min after tourniquet inflation. The averaged, normalized latencies are shown in Figure 4D. There is no apparent difference between the effects of lidocaine during normothermic and hypothermic ischemia. Recovery of distal latencies from ischemic effects occurred within 5 min. Lidocaine effects were still present 20 min after cuff deflation in all subjects ($P <$ 0.03). Amplitudes of motor responses decreased only occasionally during ischemic conditions: in 3 of 10 experiments to 42%–77% of the baseline values. After lidocaine injections, amplitudes decreased to 13%–70% of baseline levels in eight recordings; no change occurred in two recordings. Durations of motor responses were significantly prolonged (two- to threefold) only under cold conditions. Power spectrums of hypothenar EMGs showed corresponding changes: under cold conditions the main spectral energy moved from control values at 50–150 Hz to 20–60 Hz; no clear changes were observed under normothermic conditions. In lidocaine experiments, the neural failure appeared to precede changes in action potential propagation along the muscle membranes: the power spectrum of EMG showed no changes 4–5 min before cessation of voluntary movements 20 min after lidocaine injection (four recordings). After cessation of voluntary hypothenar movements, small hypothenar responses to ulnar nerve stimulation at the elbow were still obtained.

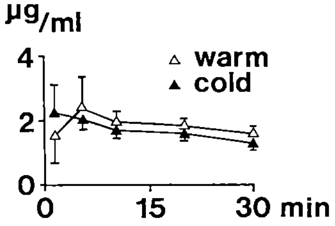


Figure 5. Mean (± SD) lidocaine plasma levels after tourniquet release.

Relationships between Sensation and Neural Responses

Anesthesia to median nerve stimulation at the palm never developed before disappearance of the median nerve potential at the elbow. In 14 experiments, where anesthesia developed or the potential disappeared, the events occurred simultaneously four times, and in 10 cases the potential disappeared first. These changes were not temperature dependent. Anesthesia to mechanical stimulation at the fingertip developed before disappearance of median nerve potentials in 10 experiments. Plexus potentials disappeared after small changes in median nerve potentials. Cervical evoked potentials peaking at 16–17 ms disappeared next, followed by the early cortical responses and then the 50–150-ms cortical responses. The 50–150-ms cortical responses disappeared later than median nerve potentials (in 10 out of 12 cases): six times simultaneously with the development of anesthesia to the stimulation, two times earlier and four times later.

Lidocaine Plasma Levels and Brain Symptoms

Lidocaine was present in blood samples taken just before tourniquet release in one subject in both experiments (warm 0.04 μg/mL; cold 0.1 μg/mL) and in another subject in the warm experiment (0.1 μg/mL). Peak individual plasma levels of between 1.68 and 4.16 μg/mL occurred 2 or 5 min after tourniquet release. There was no statistically significant difference in lidocaine concentrations between warm and hypothermic experiments.

During warm conditions, four subjects had some symptoms (for example, tinnitus, light-headedness, sleepiness) after cuff deflation, as did three subjects during hypothermia. Symptoms appeared within 1 min and disappeared by 7 min. There was no relationship between symptoms and plasma levels of lidocaine. For example, one subject reported symptoms at 0.97 μg/mL but not at 3.25 μg/mL.

Discussion

Effect of Temperature on Neural Responses by Lidocaine

A 5–10°C decrease in the nerve temperature did not accentuate the anesthetic effects of lidocaine during IVRA. Therefore, based on in vitro experiments (2), the expectation that cooling the arm would decrease time to anesthesia onset and improve the quality of block was not met. These results are consistent with a recent report that the temperature of the solution used for IVRA does not affect the rate of development or the quality of block (7). In our study, the neurophysiological data from the median nerve suggests that hypothermia slows both the development and recovery of lidocaine effects to some extent.

The main reason for a slower development of a lidocaine block under hypothermia may be reduced neural membrane penetration by the local anesthetic caused by an increase in the fraction of the ionized form of the local anesthetic molecule. Hypothermia increases the pKa of lidocaine, that is, more of it becomes ionized (8). On the other hand, the delayed block and recovery may also have been caused by a direct vasconstriction effect on the venous network of the arm, which would have restricted distribution and washout of the local anesthetic. However, we could not observe any significant differences in the washout of lidocaine as judged by the measurement of venous plasma concentrations of lidocaine. Central nervous system symptoms after tourniquet cuff release occurred during lidocaine experiments both in warm and hypothermic arms.

Relationship of the Neural Responses by Ischemia and Lidocaine to the Mode of Action of IVRA

Changes that occurred in neural responses proximal to the cuff after ischemia alone or ischemia plus lidocaine were similar to those normally observed with decreasing stimulus intensities. The results agree with the measurements during IVRA by Yamada et al. (9) and during tourniquet induced ischemia by Hari et al. (10).

Plexus potentials were lost after small changes in median nerve compound action potentials. The first cortical response, N2O, disappeared almost simultaneously with the peripheral potentials, whereas the *later* cortical responses disappeared later in quite close relationship with the loss of stimulus perception. This occurrence suggests that surgical anesthesia during IVRA will not be present until inhibition of these *later* cortical responses. The results demonstrate that neither N2O nor *later* cortical responses are very sensitive to the number or synchrony of peripheral action potentials. Similar observations have been made in patients with diabetic neuropathy (11).

Median nerve compound action potentials we recorded originate in the thickest myelinated fibers. In the lidocaine experiments, the potential always disappeared in close temporal relationship with the disapperance of stimulus sensation. Both ischemia alone and ischemia plus lidocaine abolished the radiating sensation usually elicited by electrical stimulation of sensory nerves in the palm When this took place during ischemia alone, four subjects reported that the stimulus became burning and painful. There are no such complaints in lidocaine experiments. Therefore, C-fibers may fail before A-fibers in the presence of lidocaine, as suggested by Shanks et al. (12).

Lidocaine effects on the hypothenar muscle responses to ulnar nerve stimulation were variable but less pronounced than the effects on the median nerve sensory potential. For instance, the median nerve compound action potential was lost in all lidocaine experiments, whereas the motor response to ulnar nerve stimulation was usually retained. There are several possible explanations for this difference. First, it is possible to detect a single motor unit potential, but transcutaneous detection of single neural action potentials is impossible. Second, muscular responses reflect function of nerve fibers with wider range of conduction velocities than do the sensory compound action potentials. Third, because of different spatial relationships between the signal source and recording electrodes, the amplitude of motor response is not correlated to the number of firing nerve fibers in the same way as is the compound action potential. Fourth, the differences between the median and ulnar nerve may be explained by uneven distribution of lidocaine.

Lidocaine depressed muscular responses under normothermic conditions without preceding changes in response duration or EMG power spectrum. This observation is in agreement with the view that loss of muscle function is caused primarily by motor neuron blockade (12,13). In some lidocaine experiments, voluntary movements of hypothenar musculature were not possible although a muscular response was obtained when the ulnar nerve was stimulated near the tourniquet cuff. This result may indicate a conduction block under the cuff. It is also possible that during IVRA there is a failure of sensory feedback, and collision of descending motor signals with nerve impulses generated in axons by the cuff may reflectively inhibit motor function.

Small differences in anesthetic efficacy and neurophysiological responses are detected when IVRA with lidocaine under normothermic and hypothermic conditions are compared. However, there appears to be no clinical advantage in terms of more rapid onset or improved quality of IVRA by cooling the extremity. On the contrary, hypothermia prolonged the development of the median nerve block and its recovery during IVRA with lidocaine in this study.

We thank Dr. Tapani Salmi for providing the computer programs used in the analysis of evoked potentials and power spectrum EMG. We thank Dr. Tapani Salmi and Riitta Hari for technical advice and critical comments on the manuscript.

References

1. Franz DN, Perry RS. Mechanisms for differential block among single myelinated and nonmyelinated axons by procaine. J Physiol (London) 1974;236:193–210.
2. Rosenberg PH, Heavner JE. Temperature-dependent nerve-blocking action of lidocaine and halothane. Acta Anaesthesiol Scand 1980;24:314–20.
3. Paintal AS. Block of conduction in mammalian myelinated nerve fibers by low temperatures. J Physiol 1965;180:1–19.
4. Franz DN, Iggo A. Conduction failure in myelinated and non-myelinated axons at low temperatures. J Physiol 1968; 199:319–45.
5. Mather LE, Tucker GT. Meperidine and other basic drugs: general method for their determination in plasma. J Pharm Sci 1974;63:306–7.
6. Buchtal F, Rosenfalck A. Evoked action potentials and conduction velocity in human sensory nerves. Brain Res 1966;3:1–122.
7. Paul DL, Logan MR, Wildsmith JAW. The effects of injected solution temperature on intravenous regional anaesthesia. Anaesthesia 1988;43:362–4.
8. Kamaya H, Hayes JJ, Ueda I. Dissociation constants of local anesthetics and their temperative dependence. Anesth Analg 1983;62:1025–30.
9. Yamada T, Muroga T, Kimura J. Tourniquet-induced ischemia and somatosensory evoked potentials. Neurology 1981;31: 1524–9.
10. Hari R, Perotvaara A, Kemppainen P, Salminen J. The effect of tourniquet-induced ischemia on somatically evoked cerebral magnetic fields in man. Acta Neurol Scand 1985;72:419–26.
11. Noel P. Sensory nerve conduction in the upper limbs at various stages of diabetic neuropathy. J Neurol Neurosurg Psychiatry 1973;36:786–97.
12. Shanks CA, McLeod JG. Nerve conduction studies in regional intravenous analgesia using 1 per cent lignocaine. Br J Anaesth 1970;42:1060–5.
13. Ekstedt J, Stälberg E, Thorn-Alquist A-M. Impulse transmission to muscle fibers during intravenous regional anaesthesia in man. Acta Anaesthesiol Scand 1971;15:1–2.

ANESTH ANALG
1989;69:60–8

Effects of Enflurane on Contractile Response of Canine Trachealis Muscle

Tetsuo Kochi, MD, Masato Hagiya, MD, and Tadanobu Mizuguchi, MD

KOCHI T, HAGIYA M, MIZUGUCHI T. Effects of enflurane on contractile response of canine trachealis muscle. Anesth Analg 1989;69:60–8.

The effect of enflurane anesthesia on bronchomotor tone was studied in 15 dogs, using isolated tracheal segments in situ. In six animals, the changes of tracheal tension in response to changing enflurane concentration were continuously measured while keeping tidal volume, respiratory frequency, and end-tidal PCO_2 constant. In nine other dogs, the contractile response to a brief period of apnea was assessed in three planes of anesthesia, namely 0% (baseline anesthesia with pentobarbital), 1%, and 2% of inspired enflurane concentration. In addition, effects of hypercapnia, hypoxia, and changing tidal volume were also examined in three of these nine animals. Furthermore, the magnitude of contraction elicited by electrical stimulation of the recurrent laryngeal nerve (RLN) was determined at each depth of anesthesia in six animals. Increasing enflurane concentrations invariably decreased resting tracheal tension as well as the magnitude of contraction in response to apnea and RLN stimulation in a dose-dependent manner. These data suggest that enflurane not only decreases unstimulated canine bronchomotor tone but also inhibits contraction produced by various stimuli used in the present experiments.

Key Words: ANESTHETICS, VOLATILE—enflurane. LUNG, TRACHEA—muscle tone.

Potent inhalation anesthetics are known to dilate previously constricted areas in the tracheobronchial tree. Halothane, enflurane, and isoflurane attenuate antigen-induced bronchoconstriction in sensitized canine airways (1,2). Halothane and cyclopropane also attenuate increases in pulmonary resistance (R_L) during bilateral vagus nerve stimulation in dogs (3). However, the effects of enflurane on bronchomotor tone have not been well defined.

Furthermore, the dilating effects of these anesthetic drugs on the unstimulated airway are unclear. Several investigators demonstrated dilatory effects of halothane by using either an intrabronchial probe or bronchograms, while measurement of pulmonary mechanics failed to demonstrate an appreciable decrease in R_L (4–6). These discrepancies could be explained in part by the extent of pre-existing bronchomotor tone, but may be largely due to the methods used to determine the size of airway caliber, since R_L includes not only airway resistance but also pulmonary tissue resistance. While the latter is generally believed to be a very small component, recent findings suggest that the contribution of pulmonary tissue resistance to R_L is fairly large (7,8).

Accordingly, we designed a study to evaluate the effects of enflurane on the airway smooth muscle tone using canine tracheal segments in situ and assuming that the response of trachealis muscle qualitatively represents that of central airways (9,10). Furthermore, in order to see if enflurane has some protective effects on the constrictor response of airway smooth muscle, we evaluated the magnitude of the changes in tension induced by a brief period of apnea and an electrical stimulation of recurrent laryngeal nerve, which are both known to constrict trachealis muscle (9).

Methods

The experiments were performed on 15 mongrel dogs weighing 8–19 kg. The protocol of the present study was reviewed and approved by our institutional animal investigation committee. The animals were initially anesthetized with pentobarbital (30 mg/kg, IV), and the surgical procedure was performed. A femoral vein was cannulated for administration of fluids and maintenance doses of pentobarbital (1

Received from the Department of Anesthesiology, Chiba University School of Medicine, Chiba, Japan. Accepted for publication February 7, 1989.

Address correspondence to Dr. Kochi, Department of Anesthesiology, Chiba University School of Medicine, 1–8–1, Inohana, Chiba-shi, Chiba, 280, Japan.

©1989 by the International Anesthesia Research Society

mg/kg/hr). A catheter was inserted into the femoral artery for measurement of arterial blood pressure. Body temperature was continuously monitored with a rectal thermistor and maintained at 37–38°C by means of a heater. The animals were placed in the supine position, paralyzed with pancuronium bromide (0.2 mg/kg, IV followed by 0.2 mg/kg/hr, continuous infusion), and ventilated mechanically with a volume type ventilator (AIKA EVA 900) with 100% oxygen, first through an endotracheal tube and later through a low cervical tracheotomy. At a tidal volume of 15 mL/kg, ventilatory frequency, set to keep end-tidal PCO_2 ($P_{ET}CO_2$) at 36 mm Hg, ranged from 15 to 20 breaths per min between animals. End-tidal PO_2 ($P_{ET}O_2$) was greater than 600 mm Hg in all conditions except during hypoxic challenge (see following), in which case lowest $P_{ET}O_2$ was 30 mm Hg. These baseline ventilator settings were kept unchanged throughout the experiments. Tracheal pressure (PTR), air flow ($\dot{V}$), $P_{ET}CO_2$, and $P_{ET}O_2$ were measured at the connection between the tracheotomy tube and the ventilator circuit. Changes in lung volume (ΔV) were determined by the electrical integration of the $\dot{V}$ signal.

After the cervical trachea and larynx were gently exposed, tracheotomy was performed at the lower cervical level and a J-shaped cuffed spiral tube (Rüsch) was inserted caudally. The tracheal tube was tied to the anterior chest wall and the cuff inflated to prevent air leaks. A longitudinal incision was made along the anterior margin of the trachea from the level of cartilage 4–7, and these portions were selected as the segments in which tracheal tension would be monitored. The cartilages and posterior membranes were transected at the upper and lower end of the segments, with care being taken to minimize damage to the nerves and vessels that enter the posterior surface of the muscle. The cut ends of the cartilage were tethered with nylon sutures to a metal rod on one side of the dog's neck and to a force-displacement transducer (Nihon Koden TB–611T) on the other side (Figure 1). The rod and the transducer were mounted on a rack and pinion, so that moving them both medially or laterally resulted in shortening or lengthening of the muscle fibers in the segments. Before the animals were paralyzed, the tension was adjusted to 100 g and the length of the fibers was fixed. Thus, during the course of the experiment, the force of contraction was measured isometrically. In six animals, the recurrent laryngeal nerve (RLN) was identified at the level of tracheotomy and was placed onto bipolar silver electrodes in warm paraffin for electrical stimulations. $P_{ET}CO_2$, $\dot{V}$, ΔV, PTR, blood pressure, and tracheal tension were recorded on ultraviolet-sensitive paper by a viscorder (Yokokawa). PTR, $P_{ET}CO_2$, and tension were also recorded separately on recticorder (Nihon Koden).

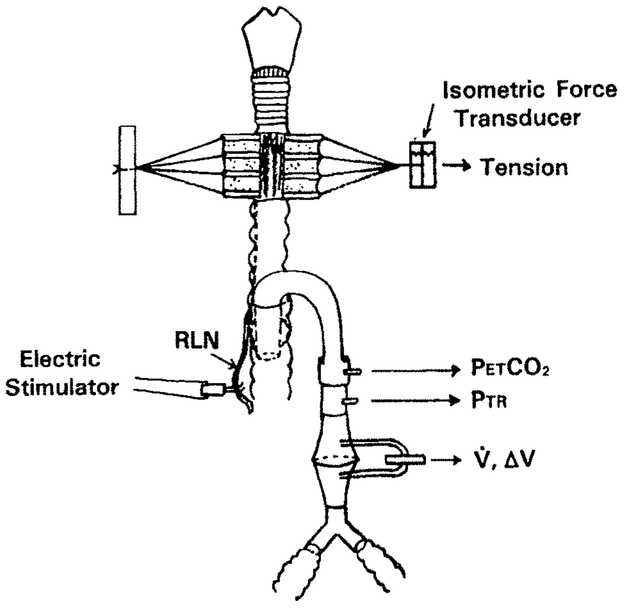


Figure 1. Schematic illustration of the preparation used in the present experiments, including RLN, recurrent laryngeal nerve, and sites for measurements of P_{TR}, tracheal pressure $\dot{V}$, airflow; ΔV, changes in lung volume; and $P_{ET}CO_2$, end-tidal PCO_2.

Experimental Procedures

Steady state experiment In six dogs, the effect of changing inspired enflurane concentration on the resting tracheal tension was examined while keeping tidal volume (V_T), respiratory frequency (f), and $P_{ET}CO_2$ constant. Because $P_{ET}CO_2$ decreases with increasing depths of anesthesia due to the reduction of CO_2 production (11), $P_{ET}CO_2$ was maintained at approximately 36 mm Hg by adding 5% CO_2 to the inspired gas. Three different enflurane concentrations, namely 1%, 2%, and 0% (control; pentobarbital alone), were used, and the sequence of changing enflurane concentrations was randomized in the six dogs. Since the tracheal tension reached a steady state level 15–20 min after changing inspired concentration, each concentration was maintained for 30 min. Recovery to the original tone was confirmed at the end of the experiment.

Apnea experiment In nine other dogs, after a period of at least 20 min of stable condition as described in steady state experiment, ventilation was halted for 1 min and the magnitude of tracheal contraction was examined at each anesthetic depth. This maneuver

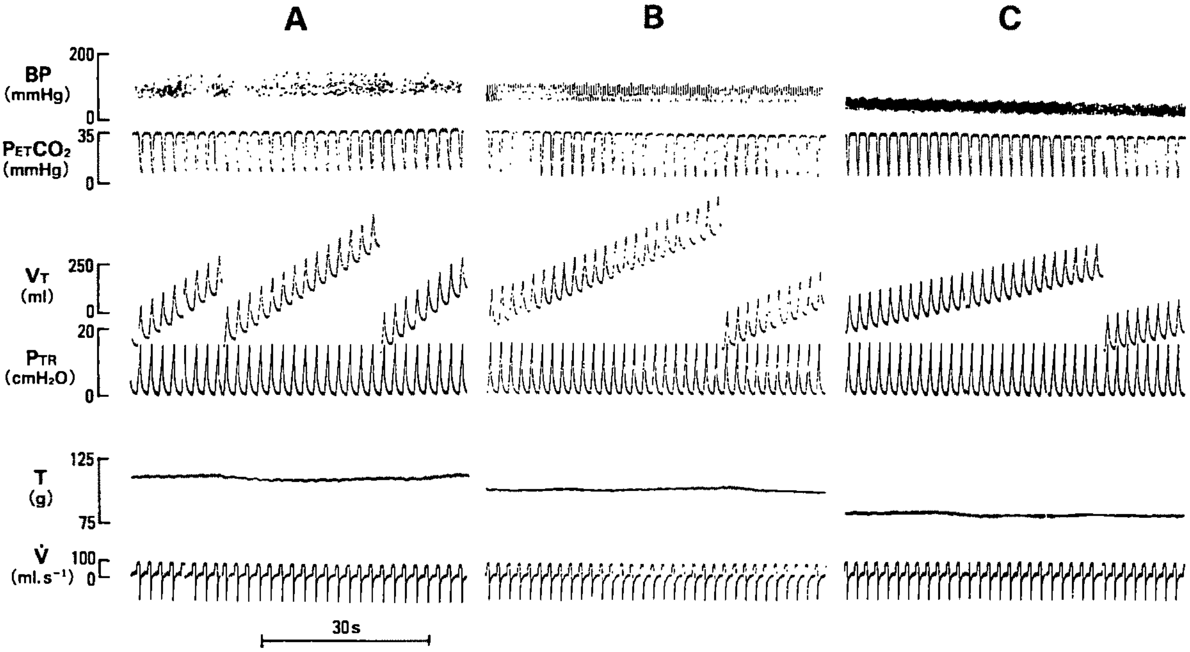


Figure 2. Representative records of arterial blood pressure (BP), end-tidal PCO_2 ($P_{ET}CO_2$), tidal volume (V_T), tracheal pressure (P_{TR}), resting tracheal tension (T) and air flow ($\dot{V}$) at various levels of enflurane anesthesia obtained in a dog. A, B, and C indicate enflurane concentration of 0%, 1%, and 2% respectively.

was repeated at least twice at 5-min intervals at each concentration of enflurane while the sequence of changing inspired concentration was randomized. In three of these nine dogs, changes of tracheal tension were also examined while abruptly changing the inspired gas from 100% O_2 to 100% nitrogen (3–4 min) or 5% CO_2–95% O_2 mixture (4–5 min) to investigate the possible role of decreasing O_2 tension or increasing CO_2 tension on the observed pattern of contraction during apnea. Furthermore, in these three animals, V_T was also reduced to about ½ of the control V_T for 4–5 min to see if changes in V_T could have some effects other than its effect through changes in $P_{ET}CO_2$. These maneuvers were accomplished under 0% enflurane following the apnea experiment and the sequence of each intervention was randomized in three animals.

RLN stimulation experiment In the remaining six of nine dogs, the experimenters' having obtained a steady condition for 20 min at each anesthetic depth, electrical stimulation of RLN was performed. This was done following the final run of the apnea experiment and the sequence of changing inspired concentrations of enflurane was randomized in each animal. RLN stimulation was applied for 30 sec by trains of square-wave pulses at a frequency of 30 Hz with a pulse duration of 3 msec and amplitude of 7 V. At least 2 sets of electrical stimulation were performed in 5-min intervals at each enflurane concentration.

Statistical Analysis

A two-way analysis of variance (ANOVA) and Tukey's test were applied for the comparison between each level of anesthesia. A P value < 0.05 was considered significant.

Results

Resting tracheal tension invariably decreased with increasing enflurane concentrations. Tracheal tension changed approximately 5 min after changing the anesthetic concentration and reached a steady state condition in 15–20 min. Figure 2 illustrates such steady state tracheal tension under various anesthetic depths obtained in a dog. In this animal, inspired enflurane concentration was changed from 1% (Figure 2B) to 2% (Figure 2C) and then to 0% (Figure 2A). The average values of resting tracheal tension for six animals at 0, 1, and 2% enflurane concentrations were 95.3 ± 21.1, 71.3 ± 19.2, and 55.6 ± 18.4 g (mean ± SE) respectively. The value obtained at 2% enflurane was statistically different from that obtained at 0% ($P < 0.05$).

Examples of the pattern of contraction during 1 min of apnea obtained in a dog under various depths

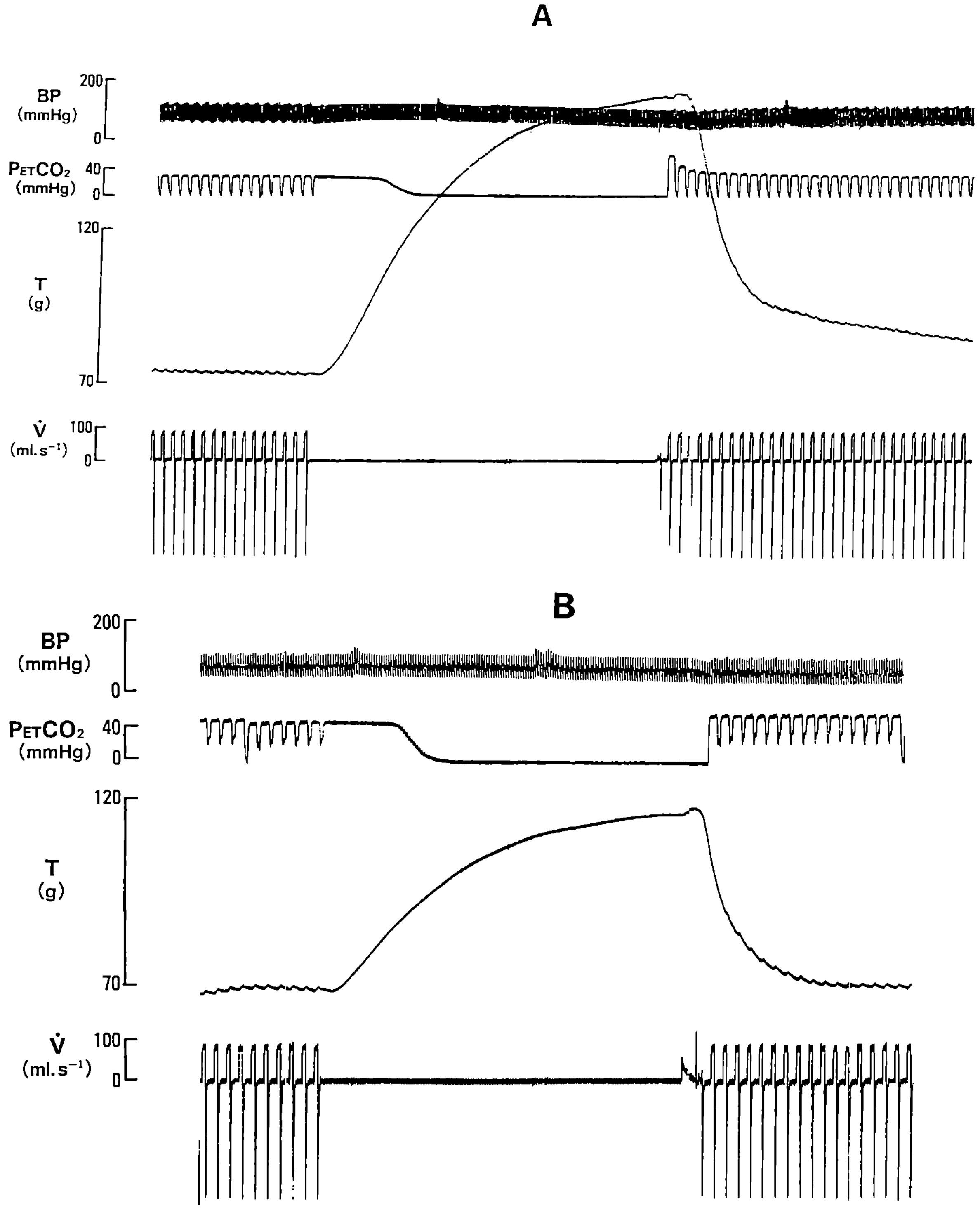
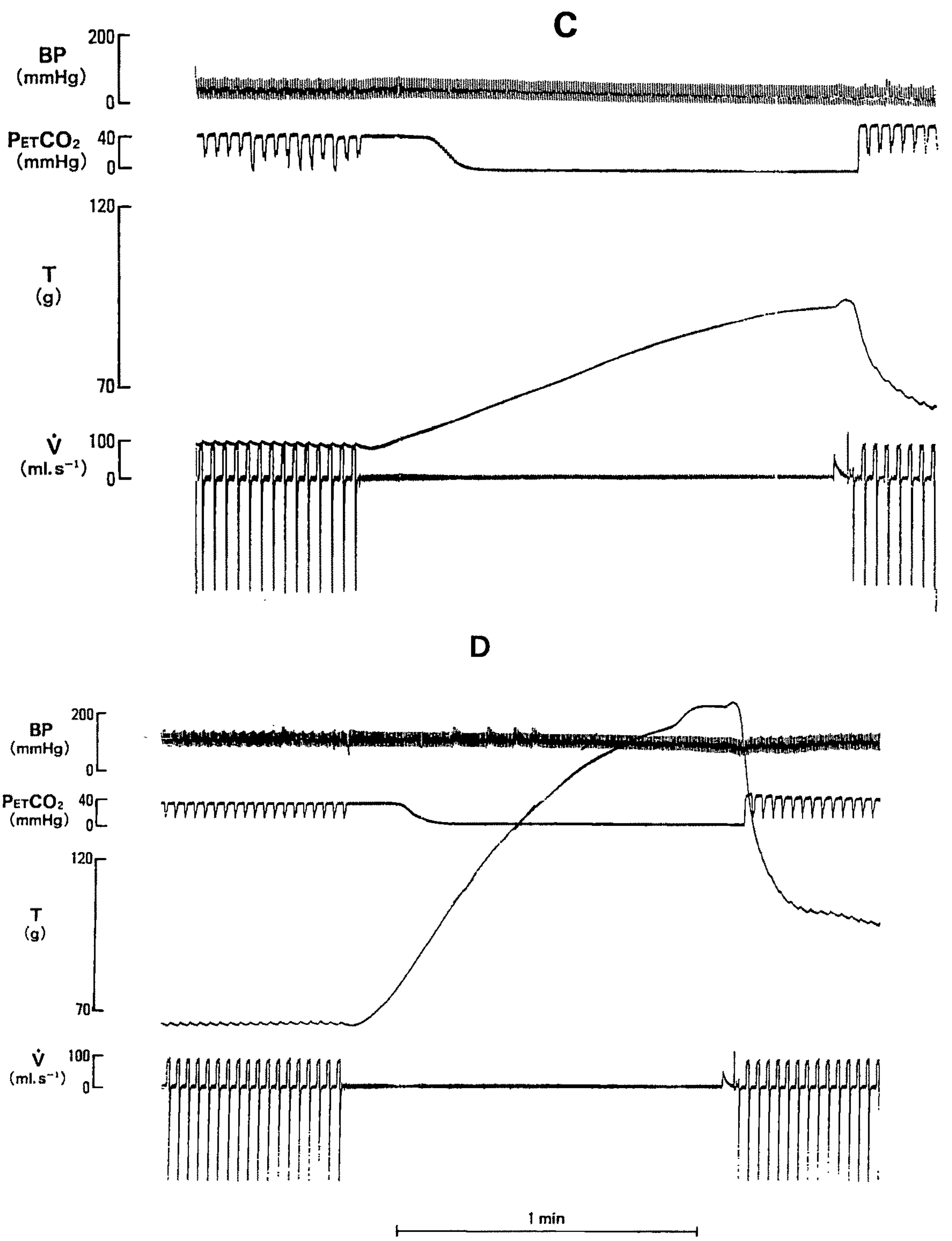


Figure 3. Experimental records demonstrating the pattern of contraction during a brief period of apnea at each depth of enflurane anesthesia in a dog. A, B, and C indicate enflurane concentration of 0%, 1%, and 2% respectively. D represents control (0%) measurement made at the end of the experiments. For definitions, see Figure 2 legends.

of anesthesia are illustrated in Figure 3. In this animal, inspired enflurane concentration was changed in the alphabetic order shown in Figure 3. The magnitude of contraction (ΔT) induced by apneic stimulation decreased with increasing the depth of enflurane anesthesia. Figure 3 also demonstrates the reversibility of the contractile response, since ΔT



obtained in the control period after enflurane washout (Figure 3D) was essentially identical to the one obtained in the initial control (0%) (Figure 3A). Table 1 illustrates the resting tension, peak tension during apnea, ΔT, and $P_{ET}CO_2$ at each level of anesthesia in nine dogs. $P_{ET}CO_2$ was maintained constant in each depth of anesthesia and, therefore, there were no statistical differences among the groups. Although differences were not statistically significant, resting tension tended to decrease with increasing the depth of anesthesia, as obtained in the steady state experiment. By contrast, increasing enflurane concentration significantly decreased ΔT in a dose-related manner. Namely, under 1% and 2% of enflurane, ΔT de-

Table 1. Mean ± SEM Values of Resting and Peak Tracheal Tension, Changes in Tension (ΔT), and End-Tidal PCO_2 ($P_{ET}CO_2$) in Apnea Experiments

Enflurane Concentration	Tracheal Tension (g)			
	Resting	Peak	ΔT (g)	$P_{ET}CO_2$ (mm Hg)
0%	76.4 ± 14.0	134.6 ± 22.0	58.2 ± 10.5	36.3 ± 0.8
1%	68.1 ± 10.0	103.3 ± 12.3	34.8 ± 9.0*	35.7 ± 0.7
2%	60.4 ± 14.4	76.7 ± 12.7	16.4 ± 4.6†,‡	36.7 ± 0.9

*$P < 0.05$ vs 0%, †$P < 0.01$ vs 0%, ‡$P < 0.05$ vs 1%.

creased by 41.6% and 72.0% from control value respectively.

The results of changing chemical drive and V_T obtained in a dog are shown in Figure 4. With changing inspired gas from 100% O_2 to 5% CO_2– 95% O_2, $P_{ET}CO_2$ increased from control value of 36 mm Hg to approximately 45 mm Hg in 2 min (Figure 4A). Reducing V_T to ½ of the control V_T resulted in similar change in $P_{ET}CO_2$ as shown in Figure 4B. Similarly, changing inspired gas from 100% O_2 to 100% N_2 resulted in a reduction of $P_{ET}O_2$ to 30–35 mm Hg in 4–5 min (Figure 4C). From these figures, it is clear that both hypercapnia (Figure 4A) and hypoxia (Figure 4C) increase tracheal tension. However, the time course and the magnitude of these changes in tension were longer and much less than those induced by 1 min of apnea. Furthermore, as shown in Figure 4B, decreased V_T resulted in a greater increase in tension with a shorter time lag, as compared to the change induced by 5% CO_2 inhalation (Figure 4A). Similar results were observed in each of the three animals studied.

Stimulation of the recurrent laryngeal nerve invariably increased tracheal tension. Figure 5 illustrates such a response. Tension started to increase with a short time delay (approximately 1–3 sec), reached a maximum in 18 ± 3 sec (mean ± SD), and returned to an initial level during electrical stimulation. PTR did not change during stimulation in either this or in all other animals, indicating no detectable changes in bronchomotor tone. Increasing enflurane concentration tended to decrease the contractile response in a dose-related fashion, while the time course of the response was not affected by enflurane. The results in all six animals are illustrated in Table 2 and Figure 6, which demonstrate dose-dependent decrease in ΔT with enflurane, and the statistical difference is noted between control and 2% ($P < 0.05$).

Discussion

The most important findings of this study include: 1) enflurane not only decreased the tension of unstimulated trachealis muscle but also attenuated the magnitude of contraction elicited by a brief period of apnea or RLN stimulation; and 2) this effect was dose-dependent. These results indicate that enflurane exerts a dilatory effect on unstimulated canine trachealis muscle, and that it has an inhibitory effect on constrictor responses induced by various stimuli used in the present experiments.

Our results of the dilatory effects of enflurane on unstimulated trachealis muscle are contrary to previous observations that demonstrate essentially no change in pulmonary resistance during enflurane or halothane anesthesia in subjects with normal bronchial tone (5,6). This discrepancy could be explained by the species difference, but also may be largely due to the difference in the methods employed to detect changes of tracheobronchial caliber. Most of the methods applied to the measurement of pulmonary resistance are conducted in nonisometric conditions and are influenced by airway geometry, edema formation, and/or mucus secretion, while the present method is used during isometric conditions and, therefore, is not influenced by changes in airway diameter. Furthermore, although pulmonary tissue resistance has been believed to be a very small component of pulmonary resistance, recent evidence suggests that the contribution of the former is fairly large, especially with small inspiratory flow rates and large tidal volumes (7,8,12). Hence the measurements of R_L may not correctly reflect the changes in airway resistance or airway caliber.

Our assumption that the isolated tracheal segments behave in a manner similar to that in more distal portions of the tracheobronchial tree may not be valid. Indeed, using a similar preparation to ours, Leff and colleagues compared sympathetic and parasympathetic contractile responses of tracheal and third-order bronchial smooth muscle simultaneously (13). They found a substantial heterogeneity between tracheal and bronchial smooth muscle in the distribution of endogenous parasympathetic and sympathetic contractile responses. Namely, relative to cholinergic contraction, α-adrenergic-mediated contraction is substantially greater in bronchi than in the trachea. Therefore, the behavior of bronchi and small bronchioles in response to enflurane might be different from that of cervical trachea. However, in the same experiment, Leff et al. found relatively similar stimulus-response curves for the trachea and bronchi using bilateral stimulation of vagus nerve. In addition, by comparing the changes of tracheal tension and R_L following pharmacologic stimulation of airway smooth muscle, Leff and his colleagues also showed that change in isometric tracheal tension is a

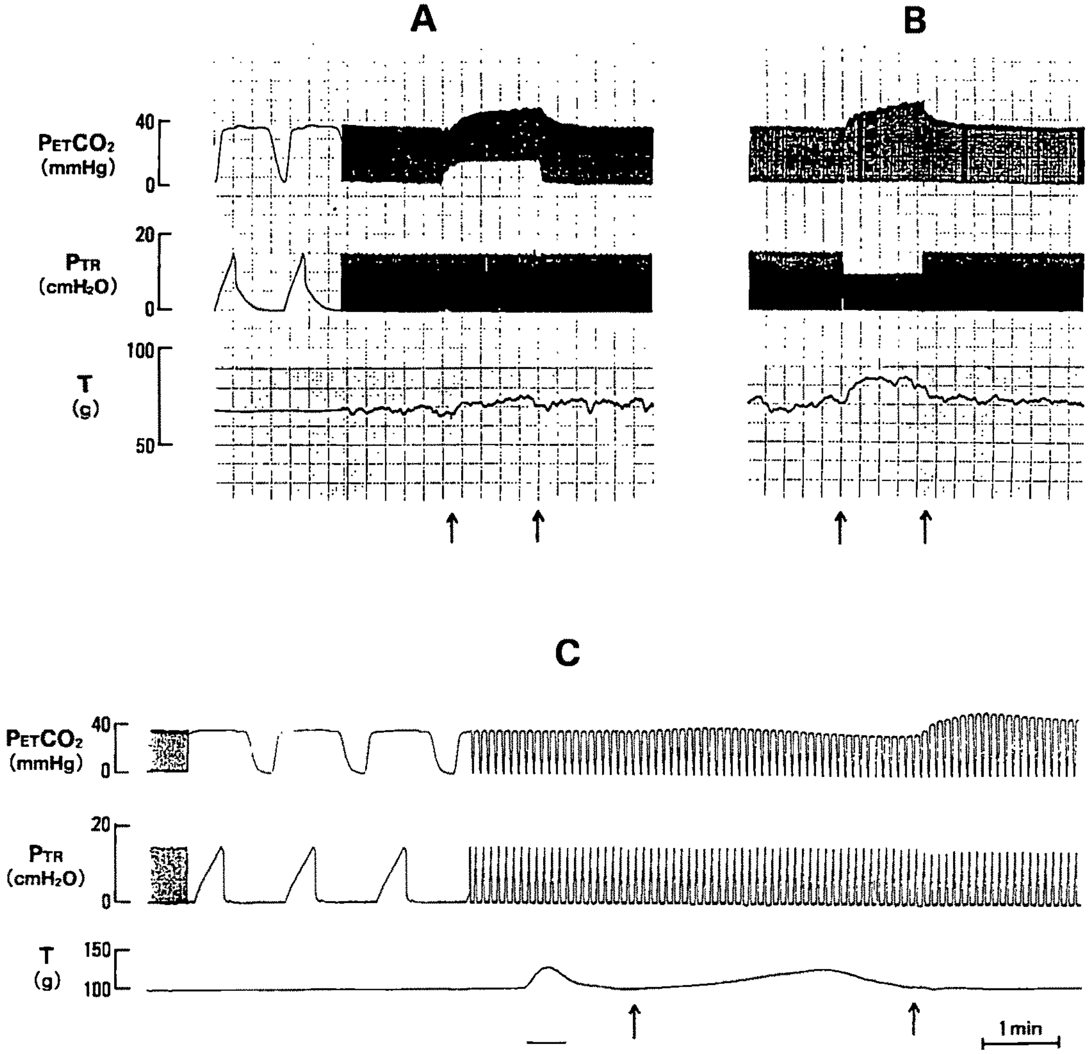


Figure 4. Characteristic changes in tracheal tension in a dog with 5% CO_2 inhalation (A), a change in tidal volume (B), and inhalation of 100% N_2 (C). Arrows indicate on and off of the changes. RLN stimulation also shown in C (underline) for comparison. For definitions, see Figure 2 legends.

more sensitive and selective measurement of airway contraction than R_L (10). Hence it would be reasonable to assume that the changes in tracheal tone reflect qualitatively the overall changes in airway resistance and airway caliber in dogs.

Neurally mediated constrictor activity of airway smooth muscle has been reported to parallel inspiratory activity in anesthetized, paralyzed animals (14,15). In this connection, enflurane is known to depress ventilation through its inhibitory effects on the respiratory center. Therefore, the present results could be explained by such a direct effect of enflurane on the central nervous system. However, our results from the RLN stimulation experiments suggest direct dilatory effects on airway smooth muscles rather than central effects, since the magnitude of contraction induced by the same stimulation parameters was depressed with increasing enflurane concentration. Several authors have reported such a direct effect of halothane and enflurane on in vitro preparation of bronchial strip (16,17). Korenaga et al. described the mechanisms of halothane-induced bronchodilation by using intracellular microelectrode and tension recordings (16). They clearly showed the direct inhibitory effects of halothane on smooth muscle cells and excitatory neuro-effector transmission. Although their results were obtained in canine trachealis muscle in vitro and with different anesthetic, similar mechanisms might be responsible for the dilatory effect of enflurane on the canine tracheal tension in situ.

In our RLN stimulation experiments, there were virtually no changes in tracheal pressure during elec-

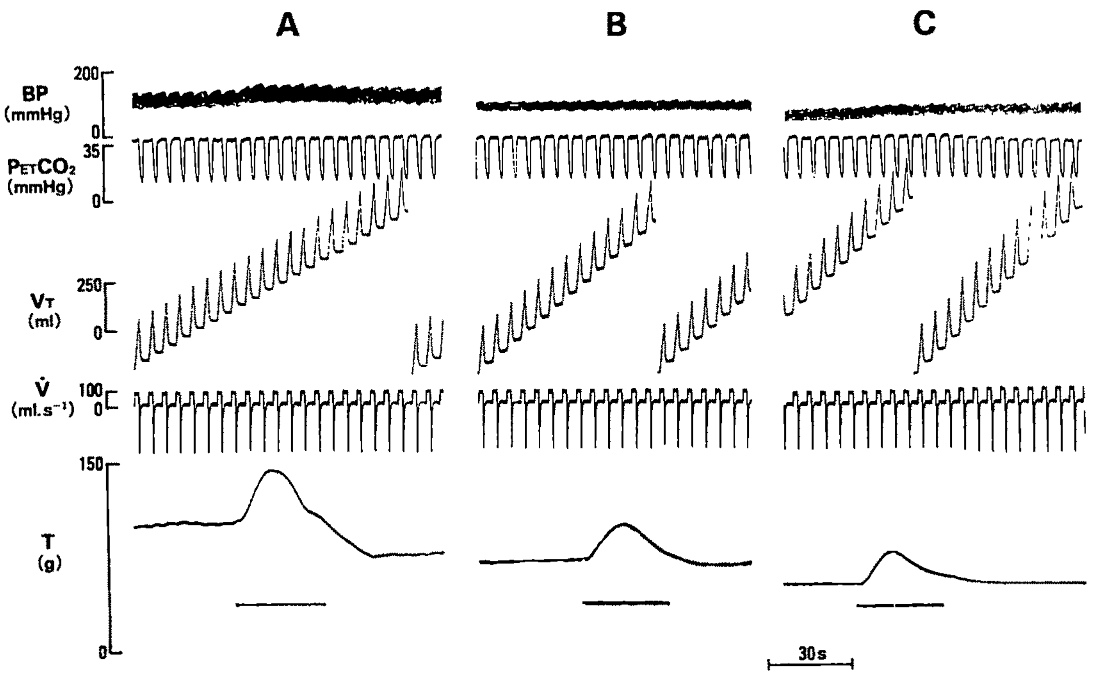


Figure 5. Changes in tracheal tension in response to electrical stimulation of recurrent laryngeal nerve at different levels of anesthesia in a dog. For definitions, see Figure 2 legends. Note the biphasic response in control and with 1% enflurane anesthesia.

Table 2. Mean ± SEM Values of Resting and Peak Tracheal Tension, Changes in Tension (ΔT), and End-Tidal PCO_2 ($P_{ET}CO_2$) in RLN Stimulation Experiments

Enflurane Concentration	Tracheal Tension (g)			
	Resting	Peak	ΔT (g)	$P_{ET}CO_2$ (mm Hg)
0%	87.4 ± 10.0	134.2 ± 15.7	46.8 ± 11.8	36.3 ± 1.2
1%	70.7 ± 6.2	101.7 ± 12.7	31.0 ± 10.9	36.6 ± 1.1
2%	63.7 ± 9.6	81.4 ± 5.5	17.7 ± 10.1*	36.2 ± 1.0

*$P < 0.05$ vs 0%.

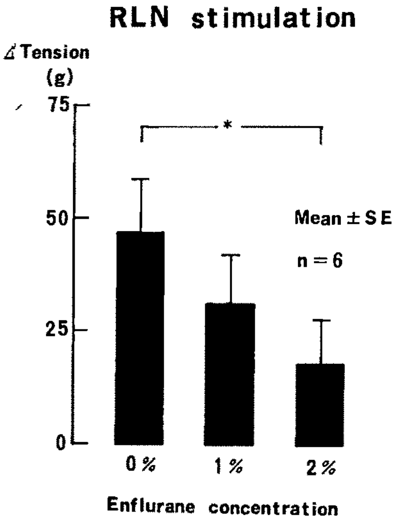


Figure 6. Changes in the magnitude of contraction (ΔT) with increasing enflurane concentration in 6 dogs. Values are mean ± SE. *$P < 0.05$ vs 0%.

trical stimulation. Since the inspiratory flow rate and tidal volume were constant, this implies that no detectable changes in respiratory resistance occurred during RLN stimulation. The lack of detectable changes is probably due to the absence of retrograde stimulation or, conversely, due to the absence of the response of bronchial tree distal to the isolated segments. However, the latter possibility is quite unlikely since, in our preliminary study, we observed an increase in PTR and decreases in heart rate and arterial blood pressure in response to electrical stimulation of vagosympathetic trunk.

As demonstrated by Brown et al. (9), the mechanisms of the tracheal contraction during a short period of apnea involve vagal afferent influences from pulmonary stretch receptor (PSR). Namely, an increase in V_T and respiratory frequency is known to stimulate slowly-adapting PSR (18) which, in turn, exerts an inhibitory effect on airway motor nerve activity. The fact that an increase in tracheal tone in response to decreasing levels of V_T is more rapid and intense than that observed during CO_2 inhalation with a similar degree of hypercapnia supports this notion. Present results also indicate that enflurane has inhibitory effects on the PSR mediated regulatory mechanisms of tracheal tone. However, it remains uncertain to what extent the activity of PSR is modified by enflurane and influences the overall changes in tracheal tension.

The implication of the present results is that enflurane decreases bronchomotor tone and inhibits contractile responses induced by various stimuli. These effects are beneficial for reduction of the work of breathing and for prevention of bronchospasm in patients with hyperreactive airways and chronic obstructive lung disease. On the other hand, decreased bronchial tone would invariably result in an increase in anatomical dead space which, in turn, could exacerbate alveolar hypoventilation induced by enflurane.

This study demonstrates that enflurane dilates both unstimulated and stimulated canine trachealis muscle in a dose-dependent fashion, and that direct action on smooth muscle cells and/or neuro-effector transmission is involved in such effects.

References

1. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H. Mechanism of action of inhalation anesthesia on airways. Anesthesiology 1982;56:107–11.
2. Hirshman CA, Bergman NA. Halothane and enflurane protect against bronchospasm in an asthma dog model. Anesth Analg 1978;57:629–33.
3. Colgan FJ. Performance of lung and bronchi during inhalation anesthesia. Anesthesiology 1965;26:778–85.
4. Hickey RF, Graf PD, Nadel JA, Larson CP Jr. The effects of halothane and cyclopropane on total pulmonary resistance in the dog. Anesthesiology 1969;31:334–43.
5. Patterson RW, Sullivan SF, Malm JR, Bowman FO Jr, Papper EM. The effect of halothane on human airway mechanics. Anesthesiology 1968;29:900–7.
6. Brakensiek AC, Bergman NA. The effects of halothane and atropine on total respiratory resistance in anesthetized man. Anesthesiology 1970;33:341–4.
7. Ludwig MS, Dreshaj I, Salway J, Munoz A, Ingram RH Jr. Partitioning of pulmonary resistance during constriction in the dog: effects of volume history. J Appl Physiol 1987;62:807–15.
8. Hoppin FG, Green M, Morgan MS. Relationship of central and peripheral airway resistance to lung volume in dogs. J Appl Physiol 1978;44:728–37.
9. Brown JK, Leff AR, Frey MJ, Reed BR, Gold WM. Physiological and pharmacological properties of canine trachealis muscle in vivo. J Appl Physiol 1980;49:84–94.
10. Leff AR, Munoz NM, Alderman B. Measurement of airway response by isometric and nonisometric techniques in situ. J Appl Physiol 1982;52:1363–7.
11. Theyne RA. The contributions of individual organ systems to the decrease in whole-body $\dot{V}O_2$ with halothane. Anesthesiology 1972;37:367–72.
12. Kochi T, Okubo S, Zin WA, Milic-Emili J. Flow and volume dependence of pulmonary mechanics in anesthetized cats. J Appl Physiol 1988;64:441–50.
13. Leff AR, Munoz NM, Hendrix SG. Parasympathetic and adrenergic contractile responses in canine trachea and bronchus. J Appl Physiol 1983;55:113–20.
14. Mitchell RA, Herbert DA, Baker DG. Inspiratory rhythm in airway smooth muscle tone. J Appl Physiol 1985;58:911–20.
15. Richardson CA, Herbert DA, Mitchell RA. Modulation of pulmonary stretch receptors and airway resistance by parasympathetic efferents. J Appl Physiol 1984;57:1842–9.
16. Korenaga S, Takeda K, Ito Y. Differential effects of halothane on airway nerves and muscle. Anesthesiology 1984;60:309–18.
17. Fletcher SW, Flacke W, Alper MH. The actions of general anesthesia on tracheal smooth muscle. Anesthesiology 1968;29:517–22.
18. Davis HL, Fowler WS, Lambert EH. Effect of volume and rate of inflation and deflation on transpulmonary pressure and response of pulmonary stretch receptors. Am J Physiol 1956;187:558–66.

Comparison of Viscoelastic Measures of Coagulation after Cardiopulmonary Bypass

Kenneth J. Tuman, MD, Bruce D. Spiess, MD, Robert J. McCarthy, PharmD, and Anthony D. Ivankovich, MD

TUMAN KJ, SPIESS BD, McCARTHY RJ, IVANKOVICH AD. Comparison of viscoelastic measures of coagulation after cardiopulmonary bypass. Anesth Analg 1989;69:69–75.

Postoperative hemorrhage remains a major cause of morbidity after cardiopulmonary bypass (CPB). Treatment remains empiric because of the need for immediate correction and the lack of availability of rapid intraoperative coagulation monitoring (except for ACT) at most institutions. Thrombelastography (TEG) and Sonoclot analysis (SCT) are measures of viscoelastic properties of blood which allow rapid intraoperative evaluation of coagulation factor and platelet activity as well as overall clot integrity from a single blood sample. Routine coagulation tests (RCT) including activated clotting time (ACT), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level (FIB), and platelet count (PLT) were determined and compared to TEG and SCT to assess which best predicted clinical hemostasis after CPB. Forty-two patients prospectively felt to be at high risk for excessive post-CPB bleeding had blood obtained for RCT, TEG, and SCT analysis before systemic heparinization and 30 min after protamine administration. Nine of 42 patients had excessive chest tube drainage, but no reoperations were required. After CPB, mean values for RCT were normal, but there were abnormalities in TEG and SCT parameters that reflect platelet-fibrin interaction. Both TEG and SCT were 100% accurate in predicting bleeding in these nine patients and, overall, both tests were significantly better predictors of postoperative hemorrhage than RCT. We conclude that viscoelastic determinants of clot strength may be abnormal after CPB and that SCT and TEG are, therefore, more useful than RCT for the detection and management of coagulation defects associated with CPB.

Key Words: BLOOD—coagulation. SURGERY—cardiovascular.

Despite technical improvements in procedures and equipment, postoperative hemorrhage remains a major cause of morbidity after cardiopulmonary bypass (CPB) necessitating surgical reexploration of the chest in approximately 3% of patients who have undergone cardiac operations (1). Evaluation of blood loss following CPB requires careful attention to the diverse details of the hemostatic competence of the patient and the nature of the surgical procedure. Although the coagulation mechanism may be normal preoperatively, major changes occur in the coagulation system during CPB. The hemorrhagic tendency after CPB is a complex reflection of multiple hemostatic defects. Coagulopathies caused by hemodilution of procoagulants, fibrinogen, and platelets are compounded by platelet abnormalities induced by drugs, oxygenators, roller pumps, and pump suction devices. After CPB, these changes may result in nonsurgical bleeding due to coagulation factor deficiency or inactivation due to heparin, platelet deficiency in quantity or quality, fibrinolysis, or disseminated intravascular coagulation (1–4).

Monitoring of coagulation and heparin therapy intraoperatively is most commonly done with the activated clotting time (ACT) or heparin assay. Postoperatively, a variety of coagulation tests are often performed to assess individual aspects of whole blood coagulation. Commonly measured parameters include the prothrombin time (PT), partial thromboplastin time (PTT), platelet count (PLT), and fibrinogen level (FIB). These tests may be augmented with measures of clot integrity such as the euglobulin lysis time or fibrin split product levels. Each of the above tests reflects isolated portions of the hemostatic sys-

---

Received from the Department of Anesthesiology, Rush–Presbyterian–St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, Illinois. Accepted for publication February 28, 1989.

Address correspondence to Dr. Tuman, Department of Anesthesiology, Rush–Presbyterian–St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, IL 60612.

©1989 by the International Anesthesia Research Society

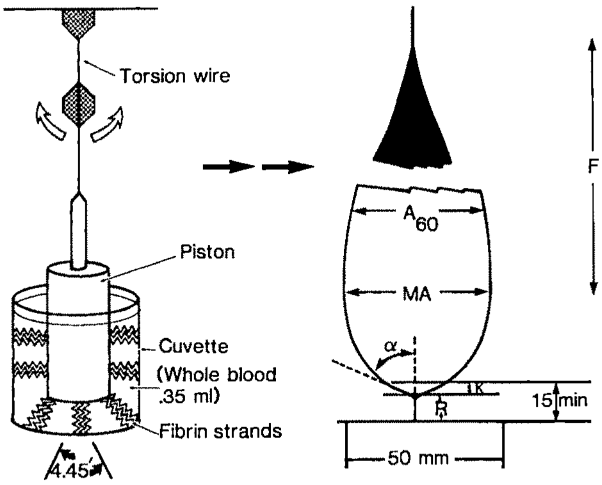


Figure 1. Production of normal thrombelastogram and measured parameters. R = reaction time, K = BiKoatugulierung or coagulation time, α = clot formation rate, MA = maximum amplitude, A_{60} = amplitude 60 min after MA, A_{60}/MA, whole blood clot lysis index, F = whole blood clot lysis time.

tem; as such no single common laboratory test routinely allows specific diagnosis of all coagulation defects, and a panel of these as well as possibly other tests are required to delineate the exact nature of a coagulopathy.

Traditional therapy for cardiac surgical patients who are bleeding still remains empiric at many institutions because of the perceived need for immediate correction of the hemostatic defect and the lack of readily available intraoperative monitors of all phases of clot formation, strength and breakdown. The administration (in some centers) of fresh frozen plasma and platelets often has little scientific basis. Because blood products are scarce, costly, and not without risk, improved monitoring in the operating room should keep inappropriate use of them to a minimum. Technology now exists to assess the intact clotting mechanism in the operating room. Thrombelastography (TEG) and Sonoclot analysis (SCT) are both methods of evaluating all phases of coagulation and allow assessment of coagulation factor, fibrinogen, and platelet activity as well as clot maturation and lysis, all from a single sample of blood (5,6). TEG and SCT are both convenient, easily performed methods of evaluating overall clot reaction and have been shown to be of clinical value in the evaluation of the hemostatic process during hepatic transplantation and cardiac surgery (7–9). Because these monitors of viscoelastic properties reflect the functionality of the overall hemostatic process, we postulated that they would be more useful in assessing coagulation after CPB than routine coagulation tests (RCT). Each RCT looks at only a small portion of the hemostatic mechanism and most RCT commonly obtained after CPB do not reflect platelet functionality. Therefore, RCT may not reflect the overall complex interactions of multiple hemostatic defects which may lead to a poorly functioning clot. The goal of this study was to compare RCT, SCT, and TEG before and after CPB to assess their accuracy in predicting clinical hemostasis.

Methods

After approval by the Institutional Human Investigation Committee, 42 adult cardiac surgical patients prospectively felt to be at high risk for excessive post-CPB bleeding gave consent to participate in this study. Patients were considered to be at high risk for bleeding if they were undergoing reoperative cardiac procedures, valve replacement, ventricular or aortic arch aneurysm resection, or other complex cardiac procedures. All patients had normal preoperative coagulation and liver function studies and none received anticoagulant or antiplatelet medications 7 days before surgery. All patients received general anesthesia with narcotics and potent inhalation agents in accordance with standard anesthetic techniques. Non–pulsatile cardiopulmonary bypass with a bubble-type oxygenator and moderate hypothermia was employed in all cases.

Blood samples for coagulation studies were drawn before systemic heparinization and 20–30 min after the final administration of protamine according to the method of Bull (10). If the ACT did not normalize with the calculated protamine dose, additional doses of protamine (25 mg, incrementally) were administered. When the total protamine dose exceeded 1.5 mg per 100 units of heparin, an in vitro protamine titration (10 mcg/mL of blood) was used to determine if the prolongation of the ACT was due to heparin or to other causes. The RCT consisted of ACT, PT, PTT, PLT, and FIB. Simultaneously, TEG determinations were performed using 0.35 mL of whole uncitrated blood and a commercially available thrombelastograph (Biclot Elvi 816 Thrombelastograph, Logos Scientific, Henderson, Nevada and Hellige Thrombelastograph, Haemoscope Corporation, Glenview, Ill). SCT determinations were similarly performed using 0.40 mL of whole uncitrated blood and a commercially available device (Sonoclot Analyzer, Sienco, Inc., Morrison, Colo).

TEG is performed by placing a small amount of whole blood (0.35 mL) in a metal cuvette, into which a piston is suspended from a torsion wire. The cuvette rotates a small amount and alterations in

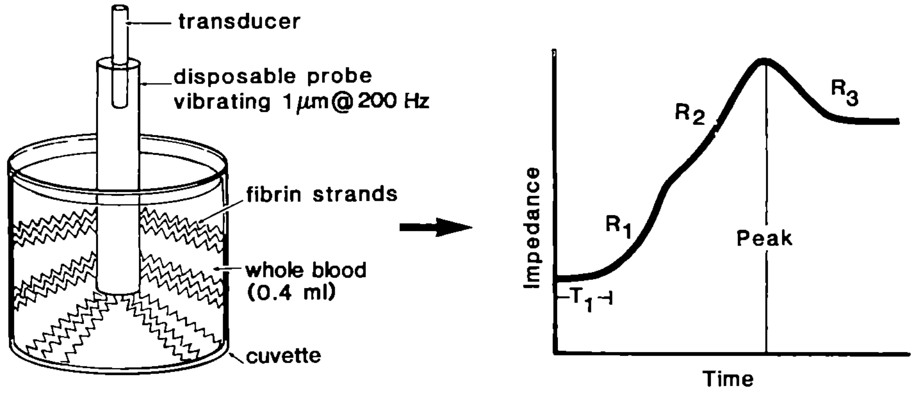


Figure 2. Production of normal Sonoclot analysis and measured parameters. T_1 = onset time, R_1 and R_2 = clot formation rate, PEAK = maximum developed impedance, R_3 = clot retraction rate.

Table 1. Coagulation Data before and after CPB

			No bleeding (N = 33)		Abnormal Bleeding (N = 9)	
	Variable	Normal Range	Before Heparin	After Protamine	Before Heparin	After Protamine
RCT						
	ACT (sec)	110–150	137.1 ± 10.1	144.6 ± 9.9	131.9 ± 7.2	142.1 ± 10.6*
	PT (sec)	10.5–12.8	11.1 ± 0.4	11.8 ± 0.9	11.0 ± 0.4	11.7 ± 0.6
	PTT (sec)	26–32	29.3 ± 2.6	32.0 ± 4.1	28.8 ± 1.6	31.6 ± 3.2
	FIB (mg/dl)	180–450	289.6 ± 44.1	216.1 ± 51.2	301.6 ± 57.9	215.9 ± 48.3
	PLT (10^3/mm^3)	150–450	256.2 ± 40.7	185.0 ± 48.6	268.7 ± 51.4	192.3 ± 51.5
SCT						
	T_1 (min)	2–6	4.4 ± 2.1	5.0 ± 2.8	3.8 ± 1.9	5.2 ± 3.3
	R_1 (mm/min)	15–30	28.6 ± 15.6	22.9 ± 12.6	27.8 ± 12.3	14.9 ± 6.3
	R_2 (mm/min)	15–30	22.3 ± 14.6	26.2 ± 13.9	28.8 ± 15.1	10.2 ± 6.2*†
	PEAK (mm)	70–90	82.8 ± 16.0	71.9 ± 13.5*	86.2 ± 12.9	57.1 ± 5.9*†
	R_3 (mm/min)	−(2–8)	−2.7 ± 2.5	−2.0 ± 1.8	−3.4 ± 2.6	−0.5 ± 0.4*†
TEG						
	R (min)	5–12	6.7 ± 2.6	9.0 ± 5.2	5.9 ± 1.9	9.3 ± 4.8
	K (min)	3–5	3.0 ± 1.1	3.6 ± 1.9	2.9 ± 1.1	4.2 ± 1.5
	α (deg)	40–60	53.4 ± 11.6	45.0 ± 11.4*	57.1 ± 10.1	36.9 ± 10.5*
	MA (mm)	50–70	53.8 ± 10.8	49.9 ± 3.2	58.2 ± 5.5	38.8 ± 9.6*†
	A_{60} (mm)	>.85·MA	49.3 ± 12.6	43.2 ± 3.4	53.8 ± 4.1	36.8 ± 9.1*

Values are means ± SD; see text for definitions.
*Value after protamine significantly different from before heparin within group, $P < 0.05$,
†Value after protamine significantly different between bleeders and nonbleeders, $P < 0.05$.

shear elasticity produced by the changing viscoelastic properties of the forming clot are transmitted through the torsion wire and measured on a recorder (Figure 1). TEG thus provides a measure of clot formation from initial procoagulant activation and fibrin formation through fibrin cross-linking and clot retraction to eventual clot sysis. Several parameters are used to describe the TEG representation of whole blood coagulation. The reaction time (R value) measures the time from placement in the cuvette until an amplitude of 1 mm is achieved and is the time necessary for initial fibrin formation. The K value is defined as the time interval from the end of R value until the amplitude of the TEG is 20 mm and is a measure of the rapidity of fibrin build-up and cross-linking. The MA, or maximum amplitude, is a reflection of the absolute strength of the fibrin clot and depends on platelet number and function as well as fibrinogen levels. The α value is measured as the slope of the outside divergence of the tracing from the point of the R value and also denotes the speed at which clot is being formed and cross-linked. The parameter A_{60} denotes the amplitude 60 min after the MA is measured. Clot lysis can be determined by measuring the amplitude as a function of time. The ratio A_{60}:MA as well as the F value (time from MA until the amplitude returns to zero) reflect loss of clot integrity due to clot lysis.

SCT is performed by placing a similar amount of whole blood (0.4 mL) into a cuvette in which a vertically vibrating probe is suspended. The changes in mechanical impedance exerted upon the probe by the changing viscoelastic properties of the forming clot are measured on a recorder and a tracing such as in Figure 2 is produced. As fibrin strands form, impedance rises at various rates until a peak impedance is achieved. The onset time (T_1) reflects the beginning of fibrin formation and the primary slope (R_1) reflects further fibrin formation and the speed at which the clot is being formed. An inflection point is often seen where the platelets first start contracting the fibrin strands. The secondary slope (R_2) reflects further fibrinogenesis and platelet-fibrin interaction. A peak impedance (PEAK) reflects completion of fibrin formation. A downward slope (R_3) is produced as platelets induce contraction of the completed clot. Therefore, platelet functionality and number are key determinants of the PEAK and R_3 values. When platelet function or number are poor, one sees a plateau rather than a peak followed by a steep R_3 due to clot contraction. Clot lysis can be determined by measuring the final impedance as a function of time (i.e., severe fibrinolysis results in a final impedance close to that at the onset of clot formation).

Measurements of the TEG parameters R, K, α, MA, A_{60}, and SCT parameters T_1, R_1, R_2, PEAK, and R_3 were performed on all samples. Excessive bleeding was defined as chest tube drainage greater than 150 mL/hr for 2 consecutive hr or greater than 300 mL/hr in 1 hr during the first 8 hr after surgery. Data for normal and abnormal postoperative hemorrhage were compared with normal and abnormal postbypass RCT, SCT, and TEG. Abnormalities of coagulation were defined as values exceeding 20% reduction from the lowest values of the normal range for FIB, PLT, α, MA, A_{60}, R_1, R_2, PEAK, and R_3, or exceeding 20% of the highest values of the normal range for ACT, PT, PTT, R, K, and T_1. Prebypass and postbypass coagulation parameters were compared using two-way analysis of variance with repeated measures in one variable. Secondary testing was performed using the Tukey-a method when necessary. The χ^2 test was used to compare the value of the various coagulation tests in predicting postoperative bleeding, assuming equal probabilities. The null hypothesis was rejected if $P < 0.05$.

Results

Table 1 compares the coagulation data of patients who experienced abnormal post-CPB hemorrhage (N = 9) to those without excessive bleeding (N = 33). Before CPB, mean values of all RCT, SCT, and TEG parameters were within normal laboratory values in both groups of patients. After CPB and administration of protamine, mean values of RCT returned to normal values in both groups although the ACT value was significantly longer compared to baseline in those patients who bled excessively. Nonbleeding patients also had normalization of SCT and TEG parameters after protamine, although peak impedance of the SCT and α of the TEG were significantly smaller than their respective prebypass values. In contrast, patients who bled excessively had abnormal values of parameters reflecting platelet-fibrin interaction (SCT: R_2, PEAK, R_3, and TEG: α, MA, A_{60}) that were also significantly different from prebypass values. Of these parameters, the R_2, PEAK, R_3, and MA values of bleeders were also significantly different than those of nonbleeders after CPB. These differences in the various coagulation parameters seen after CPB suggest that there might be a significant difference in their ability to predict clot function as reflected in abnormal postbypass bleeding.

Table 2. Accuracy of Prediction of Postoperative Hemorrhage

Coagulation Monitor	% Overall Accuracy	% False Negative	% False Positive
TEG*	88	0	15
SCT*	74	0	33
RCT	33	44	73

*TEG and SCT significantly better than RCT, $P < 0.01$.

Data on the predictive accuracy of the various coagulation monitors are presented in Table 2. After CPB, RCT were abnormal in 29 of 42 patients, but no single conventional coagulation test was consistently abnormal. Five of the 29 abnormal postbypass RCT evaluations correctly predicted bleeding, while RCT correctly predicted no bleeding in nine patients for an overall accuracy of 33% [(number of correctly predicted bleeders + number of correctly predicted nonbleeders)/42]. Fourteen of 42 patients had abnormal TEG, and 20 of 42 had abnormal SCT evaluations after protamine. The majority of the abnormalities in these tests were related to viscoelastic measures of functional platelet-fibrin interaction (TEG:α and MA; SCT: R_2, PEAK, R_3, see Table 1). The minority of abnormalities in these tests were related to coagulation factor function. There were no false negatives in predicting abnormal postbypass bleeding using TEG or SCT. There were also significantly less false positive predictions for abnormal bleeding using TEG (15%) and SCT (33%) compared to RCT (73%). Overall predictive accuracy of abnormal and normal clinical hemostasis was significantly better with TEG or SCT than with RCT (Table 2). If the criteria for

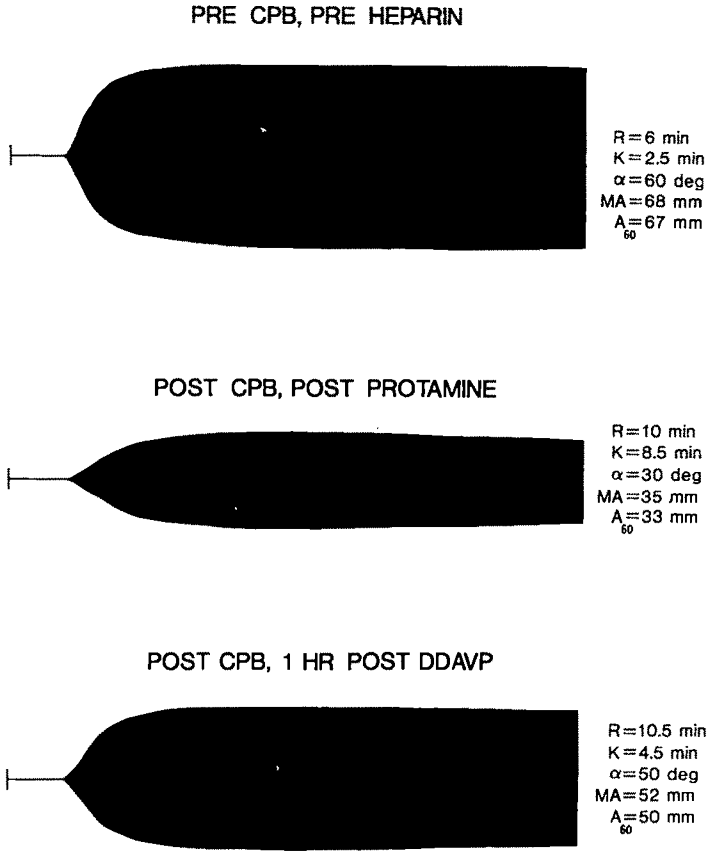


Figure 3a. Perioperative TEG analysis demonstrating normal preoperative coagulation function. After CPB and protamine administration, diminished MA and α values (demonstrating platelet dysfunction) were accompanied by excessive mediastinal bleeding. Treatment with DDAVP (0.3 mcg/kg) was associated with normalized MA and α values and cessation of bleeding. RCT were all within normal laboratory values in this patient.

predicting abnormal postsurgical hemostasis secondary to inadequate platelet number was decreased from the lower range of laboratory abnormality (150,000/mm^3 to 100,000/mm^3), there still remain 22 patients in whom RCT incorrectly predicted clinical hemostasis. The overall accuracy of RCT is then improved (20/42) but still remains <50% in predicting postoperative bleeding. There were no significant differences in the overall predictive ability, false positive, or false negative rates between TEG and SCT.

All nine patients with abnormal clinical hemostasis had coagulation therapy directed by the results of the battery of RCT, SCT, and TEG, and no patient required reoperation. No one single coagulation variable was used to guide therapy, and choice of therapy depended upon the severity of the bleeding and clinician's preference. For example, when a bleeding patient had a normal set of RCT and the SCT revealed diminished R_2, R_3, or PEAK values (with normal T_1 and R_1) or the TEG demonstrated decreased α or MA values, patients received either platelet transfusion (N = 4) or desmopressin acetate (DDAVP, N = 1). Figure 3 demonstrates the TEG and SCT patterns before CPB, after protamine administration, and after administration of DDAVP in such a patient. Prolongation of R and K values or of T_1 and R_1 values of the TEG and SCT respectively (with normal viscoelastic measures of platelet-fibrin function) prompted in vitro protamine testing on whole blood in three patients. This demonstrated improvement in TEG and SCT parameters, indicative of residual heparin effect in one patient who subsequently received more protamine; the other two patients were treated with fresh frozen plasma. One of the nine patients had TEG and SCT evidence of significant fibrinolysis, and treatment with epsilon-aminocaproic acid resulted in clinical hemostasis.

Discussion

Hemostatic abnormalities after CPB may be caused by reductions in coagulation factors, inadequate reversal of heparinization, excessive protamine administration, increased fibrinolytic activity, abnormal fibrin polymerization, thrombocytopenia, and defective platelet function. Multiple qualitative abnormalities of platelet function have been reported, including decreased platelet adhesiveness and aggregation, reduced membrane binding of alpha-adrenergic ago-

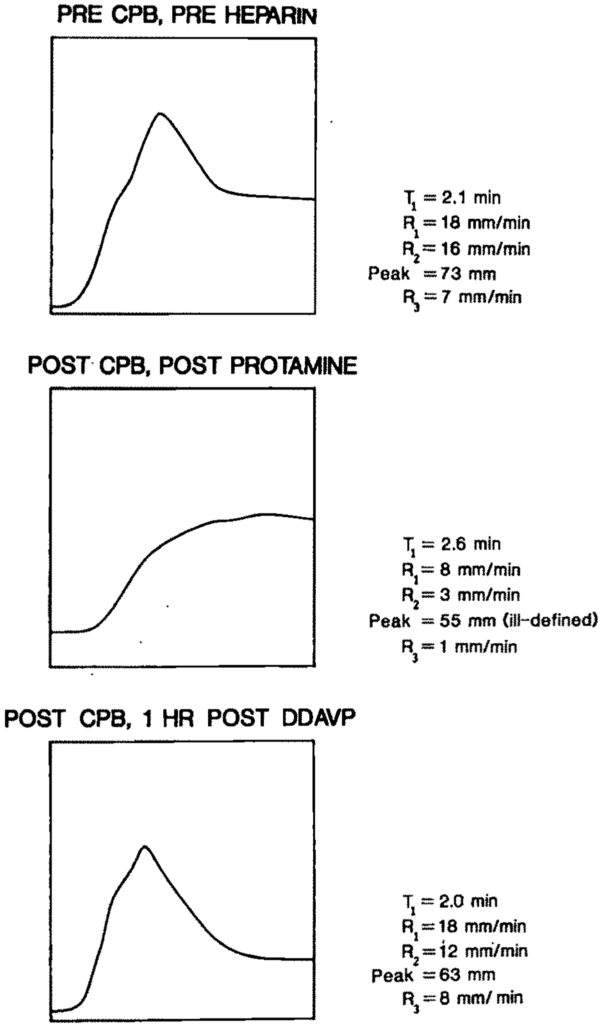


Figure 3b. Perioperative SCT analysis of same patient in Figure 3a. Preoperative SCT parameters were normal; after protamine administration R_2 and R_3 are markedly diminished, the peak is blunted and its amplitude abnormal (consistent with platelet dysfunction). Treatment with DDAVP was associated with improvement in R_2, R_3, and peak impedance.

nists and fibrinogen, and selective depletion of alpha granules (11–15). These abnormalities are primarily due to platelet activation during CPB and are compounded by hypothermia, protamine, and hemodilution. The majority of the patients in this study who exhibited a clinical hemorrhagic diathesis (5 of 9) had platelet function abnormalities demonstrated by TEG and SCT despite normal platelet counts. Other investigators have also demonstrated impairment in platelet function in patients with mediastinal bleeding after open-heart surgery despite platelet counts above 100,000/mm^3 (12). Clotting is a dynamic process which is difficult to quantitate especially when using the static endpoints of RCT which provide less information about the quality of the clot, the kinetics of its formation, and the interactions of the various components of the clotting process beyond the first stages of clotting. RCT would therefore not be expected to identify many of the causes of clot dysfunction after CPB.

TEG and SCT enable the clinician to follow a graphic record of the coagulation process and allow for diagnosis of specific problems in the hemostatic system. The greater predictive accuracy of these monitors compared to RCT probably reflects the inability of the RCT that we employed to measure viscoelastic properties of clot strength and function. RCT such as the PT, PTT, FIB, or PLT do not assess the interaction of the coagulation cascade with the platelet surface, which is altered during CPB (11–15). Perhaps use of template bleeding times, platelet function tests, euglobulin lysis times, or fibrin degradation products would provide more useful information about clot integrity. However, these tests are not regularly performed in the operating room after protamine reversal and each of them gives a limited view into the clotting process. Both SCT and TEG provide rapid evaluation of all phases of coagulation activity from a single sample of blood, on-site in the operating room. This allows rapid goal-directed therapy of postbypass coagulation defects. Such therapeutic interventions can be instituted more rapidly than those based on tests performed at sites distant from the operating room. The convenience of on-site use by anesthesia personnel combined with better accuracy in predicting clinical hemostatic function should reduce the morbidity associated with post-CPB bleeding as well as the need for empiric therapy with blood products that are costly and carry the risk of infectious complications.

Our data suggest that SCT and TEG monitoring of coagulation are reliable predictors of abnormal clinical hemostasis after CPB that provide evaluation of the coagulation process from onset through clot lysis, allowing appropriate guidance of therapy in the postbypass period. Further controlled studies are necessary to demonstrate the effectiveness of these viscoelastic measures of coagulation in reducing blood product usage after cardiac surgery.

References

1. Salzman WE, Weinstein MJ, Weintraub RM, et al. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. N Engl J Med 1986;314:1402–6.
2. Mammen EF, Koets MH, Washington BC, et al. Hemostasis changes during cardiopulmonary bypass surgery. Semin Thromb Hemost 1985;11:281–92.
3. Bick RL. Alterations of hemostasis associated with cardiopulmonary bypass: pathophysiology, prevention, diagnosis and management. Semin Thromb Hemostas 1976;3:59–82.

4. Moriau M, Masune R, Hurlet A, Ponlot CC. Haemostasis disorders in open heart surgery with extracorporeal circulation. Vox Sang 1977;32:41–51.
5. Spiess BD, Ivankovich AD. Thromboelastography: a coagulation-monitoring technique applied to cardiopulmonary bypass. In: Ellison N, Jobes DR, eds. Effective hemostasis in cardiac surgery. Philadelphia: WB Saunders, 1988:163–81.
6. Shenaq SA, Saleem A. Viscoelastic measurement of clot formation: the Sonoclot. In: Ellison N, Jobes DR, eds. Effective hemostasis in cardiac surgery. Philadelphia: WB Saunders, 1988:183–93.
7. Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985;64:888–96.
8. Spiess BD, Tuman KJ, McCarthy RJ, Ivankovich AD. Thrombelastography as an indicator of post-cardiopulmonary bypass coagulopathies. J Clin Monit 1987;3:25–30.
9. Saleem A, Blifeld C, Saleh SA, et al. Viscoelastic measurement of clot formation: a new test of platelet function. Ann Clin Lab Sci 1983;13:115–24.
10. Bull B, Huse W, Brauer F, et al. Heparin therapy during extracorporeal circulation. II. The use of a dose-response curve to individualize heparin and protamine dosage. J Thorac Cardiovasc Surg 1975;69:685–9.
11. Bick RL. Hemostasis defects associated with cardiac surgery, prosthetic devices, and other extracorporeal circuits. Semin Thromb Hemost 1985;11:249–80.
12. Harker LA, Malpass TW, Branson HE, Hessel EA II, Schlichter SJ. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective alpha-granule release. Blood 1980;56:824–34.
13. Beurling-Harbury C, Galvan CA. Acquired decrease in platelet secretory ADP associated with increased postoperative bleeding in post–cardiopulmonary bypass patients and in patients with severe valvular heart disease. Blood 1978;52:13–23.
14. Musial J, Niewiarowski S, Hershock D, Morinelli TA, Colman RW, Edmunds LH Jr. Loss of fibrinogen receptors from the platelet surface during simulated extracorporeal circulation. J Lab Clin Med 1985;105:514–22.
15. Wachtfogel YT, Musial J, Jenkin B, Niewiarowski S, Edmunds LH Jr, Colman RW. Loss of platelet alpha$_2$-adrenergic receptors during simulated extracorporeal circulation: prevention with prostaglandin E_1. J Lab Clin Med 1985;105:601–7.

76 ANESTH ANALG
1989;69:76–80

Differing Effect of Agonist and Antagonist Muscle Relaxants on Cat Jaw Muscles

A. F. L. Van Der Spek, MD,[*] P. I. Reynolds, MD,[*] J. A. Ashton-Miller, PhD,[†]
C. S. Stohler, DDS,[‡] and M. A. Schork, PhD[§]

VAN DER SPEK AFL, REYNOLDS PI, ASHTON-MILLER JA, STOHLER CS, SCHORK MA. Differing effect of agonist and antagonist muscle relaxants on cat jaw muscles. Anesth Analg 1989;69:76–80.

Mouth closure and an increased resistance to mouth opening follow succinylcholine administration in humans. To elucidate the effects of succinylcholine on masticatory muscle function, mouth opening in the cat, produced by a constant test force, was measured during steady state halothane anesthesia. After baseline measurements, either succinylcholine (0.3 $mg \cdot kg^{-1}$ of body weight) or vecuronium (0.1 $mg \cdot kg^{-1}$ of body weight) was infused intravenously, and mouth opening measurements were repeated for up to 30 min. Concomitantly, muscle relaxant effect was quantified by measurement of the neurally-evoked tibialis anterior muscle response. All animals given succinylcholine displayed active jaw closure, which was followed by an increased resistance to mouth opening. This increased resistance was present after cessation of fasciculations and during complete twitch suppression. It lasted beyond the time at which the limb muscle twitch had fully recovered. Vecuronium administration was associated with a decreased resistance to mouth opening without a closing action. The initial jaw closure and the subsequently increased resistance to mouth opening after succinylcholine administration during halothane anesthesia in the cat are comparable with mouth opening changes after succinylcholine administration during inhalation anesthesia in humans. The cat may serve as an animal model for study of the mechanisms involved in responses of jaw muscles to succinylcholine with use of techniques inappropriate in humans.

Key Words: ANESTHETIC, VOLATILE—halothane. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE—vecuronium.

Succinylcholine administered intravenously in doses of 1–2 mg/kg of body weight during halothane or enflurane anesthesia in humans is associated with an increase rather than a decrease in resistance to mouth opening. Vecuronium administration under the same circumstances is not associated with mouth opening changes (1,2). It is desirable to identify an animal that exhibits a similar response following succinylcholine and vecuronium administration during inhalation anesthesia to permit the elucidation of the mechanism(s) underlying this unexpected response. Therefore, we studied the resistance to mouth opening after the administration of succinylcholine and vecuronium in the cat.

The cat was chosen as an experimental animal because it is frequently used for the study of muscle relaxants and, therefore, much is known about relaxant dosages and their effects on limb muscles. Halothane anesthesia was chosen as the inhalation agent because it had provided the conditions for demonstration of the response in humans, and it is well tolerated in cats. Furthermore, depth of anesthesia with an inhalation technique is simple to control and quantify in terms of a steady state end-tidal level, whereas anesthetic depth in the cat is less well defined during intravenous techniques with, for example, α-chloralose. The mouth opening techniques used in the human studies were duplicated in the experimental animal to reproduce the same type of measurement and, perhaps, responses as documented in humans.

Methods

The following study was approved by the University's Committee on Use and Care of Animals. Adult cats of either sex were obtained from the University's

---

Received from the *Department of Anesthesiology; †Department of Mechanical Engineering and Applied Mechanics; ‡School of Dentistry; and §School of Public Health, University of Michigan, Ann Arbor, Michigan. This study was presented at the 1988 Annual Meeting of the Canadian Anaesthetists' Society, Halifax, N.S., Canada, June, 1988. Accepted for publication January 26, 1989.

Address correspondence to Dr. Van Der Spek, Department of Anesthesiology, The University of Michigan, C. S. Mott Children's Hospital, Room C4139, Box 0800, Ann Arbor, MI 48109-0800.

©1989 by the International Anesthesia Research Society

Laboratory of Animal Medicine. They were in good health. Food and water were not withheld, and they were not treated with antibiotic medication. General anesthesia with halothane in oxygen was induced in an induction chamber. At a deep level of anesthesia, cats were transferred to the operating room table and placed in the dorsal recumbent position. Under direct laryngoscopy, the trachea was intubated orally during spontaneous respirations with a 4.5-mm endotracheal tube. The tracheal tube was securely fastened just lateral to the left maxillary canine. Ventilation was controlled with an anesthesia ventilator (Air-Shields Inc., Hatboro, PA and Ohio Medical Products, Madison, WI) utilizing a circle system with soda lime absorber and a halothane vaporizer (Fluotec Mark 3, Cyprane North America Inc., Tonawanda, NY). End-tidal levels of carbon dioxide (CO_2) and halothane were measured by a calibrated infrared spectrometer (ACE, Sensors Inc., Ann Arbor, MI). Normocarbia for cats was maintained with a stable end-tidal level of 2.5% halothane. The femoral artery and vein were exposed and cannulated through incisions in the right inguinal region. Arterial pressures were transduced, and arterial blood gas tensions were determined intermittently to maintain the partial pressures of oxygen, carbon dioxide, and the pH within the normal range for cats (3). A balanced electrolyte solution was infused intravenously. The electrocardiogram was recorded via needle electrodes. Body temperature was measured with a rectal thermistor probe (Yellow Springs, OH), which also served as the feedback loop for infrared heating lamps to maintain a normal body temperature of 38.5–39°C (3).

The skin overlying the left hind leg was incised from the area of the femoral trochanter down to the popliteal space. The muscles overlying the sciatic nerve were bluntly parted along their fascial plane and the sciatic nerve was transected at the level of the femoral trochanter. Platinum electrodes were placed at the tibial branch of the sciatic nerve in the popliteal space. After irrigation, the muscles and skin were reapproximated to prevent heat loss and drying of the nerve. The tibial nerve was stimulated with supramaximal, square wave pulses of 0.2 ms duration at a rate of 1 Hz, delivered via a stimulus isolation unit (S88 Stimulator and SIU #5, Grass Medical Instruments, Quincy, MA). The relatively high frequency of stimulation was chosen to describe the masticatory muscle phenomena with a better time resolution than would be attainable with a stimulus frequency of 0.1 Hz. Thus, the timing of onset, duration, and offset of the effects of muscle relaxants may not be directly comparable with timing obtained with different stimulus frequencies. The tibia was fixed with Steinman pins in a rigid frame, which allowed isometric contractions of the left anterior tibialis muscle. The tendon of the anterior tibialis muscle was surgically exposed at the dorsum of the left foot. It was freed and transected distal to the proximal retinaculum extensorum and attached, with nonstretchable suture material, to an isometric force transducer (FT10, Grass Medical Instruments, Quincy, MA). The force transducer was contained in the rigid frame. The physiological signals of the transducers were amplified, displayed, and recorded (Gould Brush 2400, Gould Instruments, Cleveland, Ohio). Following determination of the supramaximal stimulus level and the optimal pre-load, the preparation was allowed to stabilize for a minimum of 10 min. Total preparation took approximately 45 min during which time the end-tidal halothane concentration stabilized at 2.5%.

The cat's head was immobilized on the operating table. Mouth opening was produced by the application of a constant force of 0.835 Newton to the mandible (Neg'ator Motor™, McMaster-Carr, Elmhurst, IL). The force was directed in the mid-sagittal plane at a 90° angle to the mandibular plane. The resulting separation of the maxillary and mandibular incisors was measured in the mid-sagittal plane. This method is analogous to that reported earlier for humans (1). After baseline measurements, either succinylcholine 0.3 $mg \cdot kg^{-1}$ or vecuronium 0.1 $mg \cdot kg^{-1}$ was injected as a bolus in the iliac vein. These doses of succinylcholine and vecuronium are approximately equipotent (2.5 times the ED-95) in depressing the neurally evoked limb muscle twitch in cats following intravenous administration (4–6). The magnitude of the doses were chosen to ensure flaccidity of all limb and abdominal muscles. The relaxants were randomly assigned to the experimental animals. Mouth opening measurements were obtained at intervals of 30 sec for the first 10 min and at 1 min intervals during the next 20 min.

Body weights of the two groups of cats were compared by analysis of variance (ANOVA). To assess whether either muscle relaxant had a significant effect on mouth opening over time within each group, baseline mouth opening was compared by one population repeated measures ANOVA (op-rm-ANOVA) to that at 1, 10, 20, and 30 min after muscle relaxant administration. Mouth opening after administration of the two relaxants at 1, 10, 20, and 30 min was compared by ANOVA. Because of variation in baseline, opening measurements were also expressed in each animal relative to their baseline value (normalization). Between-group comparisons at 1,

Table 1. Comparisons of Mean Mouth Opening (in mm and in values normalized with respect to their baseline) in the Cat during Halothane Anesthesia (2.5% end-tidal) after Intravenous Succinylcholine (0.3 $mg{\cdot}kg^{-1}$) or Vecuronium (0.1 $mg{\cdot}kg^{-1}$) Administration

Relaxant	n	Baseline	1 min	10 min	20 min	30 min
		Mouth Opening (mm)				
Succinylcholine 0.3 $mg{\cdot}kg^{-1}$	6	35.1 ± 2.4	18.3 ± 6.4	27.3 ± 6.4	27.9 ± 5.8	29.6 ± 4.83*
Vecuronium 0.1 $mg{\cdot}kg^{-1}$	6	30.6 ± 1.8	31.8 ± 2.6	32.2 ± 2.4	32.2 ± 2.4	32.3 ± 1.72†
ANOVA		F = 12.6 $P < 0.01$+	F = 19.7 $P < 0.005$+	F = 2.7 $P < 0.13$	F = 2.4 $P < 0.15$	F = 1.67 $P < 0.22$
		Mouth Opening Normalized With Respect to their Baseline				
Succinylcholine 0.3 $mg{\cdot}kg^{-1}$		1	0.52 ± 0.17	0.77 ± 0.14	0.79 ± 0.14	0.82 ± 0.13*
Vecuronium 0.1 $mg{\cdot}kg^{-1}$		1	1.04 ± 0.04	1.05 ± 0.04	1.05 ± 0.04	1.05 ± 0.04†
ANOVA			F = 43.3 $P < 0.0004$+	F = 17.6 $P < 0.01$+	F = 17.0 $P < 0.01$+	F = 14.2 $P < 0.02$+

*One population repeated measures ANOVA indicated the values at 1, 10, 20, and 30 min to differ significantly from baseline in the group receiving succinylcholine (F = 35.2, $P < 0.001$, corrected for pairwise multiple comparison). †the values at 10, 20, and 30 min differed from those at baseline in animals receiving vecuronium (F = 5.1, $P < 0.03$, corrected for pairwise multiple comparison). Mouth opening values between groups were compared by ANOVA; + = indicates corrected for pairwise multiple comparison according to Bonferroni equation. Values are expressed as mean ± SD.

10, 20, and 30 min were repeated by ANOVA. To compare all changes in mouth opening over time among the two muscle relaxant groups, a profile analysis was obtained by fitting a polynomial function in each cat to the mouth opening values after muscle relaxant administration. After standardization and correction for multicollinearity, the coefficients of the polynomial functions of both groups were then compared by multivariate analysis of variance (MANOVA) and ANOVA.

Results

The two groups of experimental animals did not differ significantly ($P > 0.05$) with respect to their weight (succinylcholine: 3.0 ± 0.34 kg, n = 6; vecuronium: 3.3 ± 0.86 kg, n = 6, mean ± SD).

A considerable variation of baseline mouth opening was present with a range of 32–40 mm in the animals receiving succinylcholine and a range of 28–33 mm in those receiving vecuronium (Table 1). Initial active jaw closing with the mandibular premolars impinging onto the endotracheal tube was observed in all animals receiving succinylcholine, but in none of the animals receiving vecuronium. This initial jaw closing began during the development of neuromuscular blockade and the period of fasciculations.

The one-population rm-ANOVA demonstrated vecuronium administration to be associated with a small, but significant increase in mouth opening at 10, 20, and 30 min compared with baseline values (Table 1). Significant mouth opening reductions were demonstrated in the animals receiving succinylcholine during complete suppression of the anterior tibialis muscle twitch after completion of fasciculations (1 min), during recovery (10 min), and after full recovery to control twitch height (20 and 30 min) (Table 1). Between-group comparison of the absolute mouth opening values at these times demonstrated significant differences only during the first 10 min of the experiment. However, the between-group differences of normalized mouth opening were significant at these four times following relaxant administration (Table 1).

The changes in mean normalized mouth opening are depicted in Figure 1 for both muscle relaxant groups. Mouth opening following muscle relaxant administration was described by a third order polynomial function. The polynomial functions for the group receiving succinylcholine differed significantly from those describing mouth opening in animals receiving vecuronium (Table 2).

Limb and abdominal muscles were flaccid during anterior tibialis twitch-ablation, which was obtained in all cats. The mean time to complete suppression of the neurally-evoked anterior tibialis muscle response was 21.4 ± 8.4 sec (mean ± SD) in the group receiving succinylcholine and 124.0 ± 52.5 sec (mean ± SD) in the animals receiving vecuronium. All animals receiving succinylcholine exhibited fasciculations; the second mouth opening measurement (at 30 sec) was taken after cessation of fasciculations and after loss of the evoked twitch except in one animal that lost its twitch at 34 sec. The mean time to the return of the

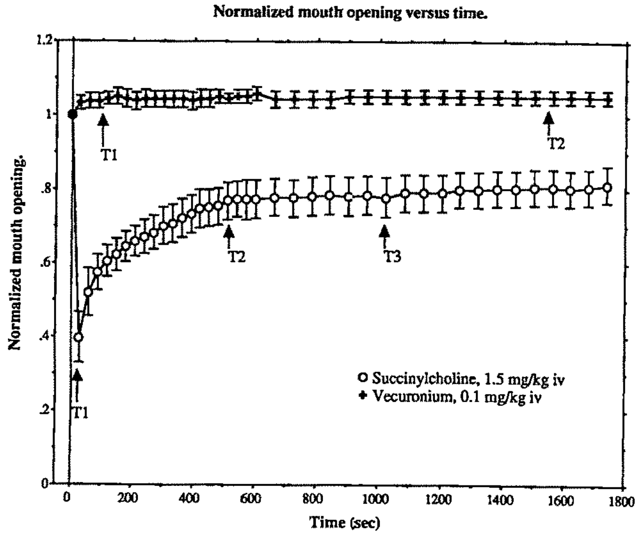


Figure 1. Mean feline mouth opening after intravenous succinylcholine (0.3 mg·kg^{-1}) or vecuronium (0.1 mg·kg^{-1}) administration during general anesthesia with halothane (2.5% end-tidal level). The ordinate represents the normalized mouth opening, which was obtained by expressing each opening relative to its baseline. The abscissa presents time in sec. Standard error bars are provided for the mean values of each group. The mean time to complete suppression of the neurally-evoked anterior tibialis twitch (T_1), to return of the first twitch (T_2) and to full recovery of control twitch height (T_3) are given. Opening measurements were started in five out of six cats receiving succinylcholine after cessation of fasciculations and during complete suppression of the evoked twitch.

first twitch was 513 ± 112 sec and to full recovery of control twitch height 1016 ± 92 sec (mean ± SD) in the animals receiving succinylcholine. The first twitch of the vecuronium group returned in 1547 ± 512 sec. Vital signs and end-tidal carbon dioxide levels remained stable throughout the experiments, whereas radiant heating was intermittently required in all animals to avoid hypothermia.

Discussion

In this study, a paralyzing dose of the depolarizing muscle relaxant, succinylcholine, administered to the cat during halothane anesthesia was followed by jaw closure. After fasciculations and during complete inhibition of neuromuscular transmission, an increase rather than a decrease in resistance to mouth opening was demonstrated in all animals. It resulted in a reduced, rather than an increased, mouth opening, which outlasted the duration of succinylcholine's inhibition of neuromuscular transmission in the cat's limb muscle. Administration of the nondepolarizing relaxant, vecuronium, was followed by a reduced resistance to mouth opening and resulted in an increased mouth opening. Mean mouth opening at baseline in cats receiving vecuronium was smaller than that observed in the group of cats receiving succinylcholine. The reason for this difference is unknown.

During halothane anesthesia in children, administration of succinylcholine (1–2 mg·kg^{-1}, IV) led to an increased resistance to mouth opening (1). A smaller rather than a larger mouth opening resulted in all subjects following the loss of the neurally-evoked adductor pollicis twitch. Vecuronium (0.1 mg·kg^{-1}, IV) administration was not followed by mouth opening reductions (1). During enflurane anesthesia in children, administration of succinylcholine (1.5 mg·kg^{-1}, IV), unlike vecuronium (0.1 mg·kg^{-1}, IV), was also followed by an increased resistance to mouth opening (2). This increased resistance occurred during limb and abdominal muscle flaccidity, during complete suppression of the indirectly evoked twitch of the adductor pollicis muscle, and after cessation of fasciculations and spontaneous respiration (2). In a number of subjects, the increased resistance persisted beyond the return of the indirectly evoked adductor pollicis twitch (2). Therefore, the timing of the increased resistance found after succinylcholine administration in the cat appears similar to that observed in these human studies.

In a recent study by Leary and Ellis (7), jaw closing forces have been recorded in humans after the intravenous administration of succinylcholine. After induction of general anesthesia with thiopental (4–6 mg·kg^{-1}, IV), a bite plate-like device, placed between the central incisors of human adults, permitted continuous recording of bite forces developed. Within the first min after administration of succinylcholine, jaw closing forces of up to 2.4 kgf were recorded, whereas muscle fasciculations and loss of the neurally evoked twitch of the adductor pollicis muscle occurred at the same time. This human jaw closing action may be analogous to the jaw closing and impingement of the tracheal tube observed in the cat after succinylcholine administration.

Relaxant doses of succinylcholine and vecuronium were chosen to be approximately equipotent in the cat and to induce flaccidity of the limb muscles with complete inhibition of neuromuscular transmission. This choice of relaxant dosage is analogous to their use in humans and to that of the previously mentioned human studies (1,2). The dose of succinylcholine administered to the cat to induce flaccidity for a few (5–10) min is lower than that ordinarily used in humans, because feline plasma cholinesterase is less efficient in hydrolyzing succinylcholine than human plasma cholinesterase. We conclude that the cat war-

Table 2. Comparison of the Polynomial Functions Describing Mouth Opening Changes Over Time after Intravenous Vecuronium or Succinylcholine Administration during Halothane Anesthesia in the Cat

Relaxant	n	Constant	Coefficient 1	Coefficient 2	Coefficient 3
Succinylcholine 0.3 $mg \cdot kg^{-1}$	6	16.5 ± 4.9	0.035 ± 0.01	−3.42E-5 ± 9.83E-6	1.05E-8 ± 3.016E-9
Vecuronium 0.1 $mg \cdot kg^{-1}$	6	31.8 ± 2.5	0.001 ± 0.004	−6.83E-7 ± 5.17E-6	1.181E-10 ± 1.74E-9
ANOVA		F = 39.5 $P < 0.0004$*	F = 53.2 $P < 0.0002$*	F = 47.9 $P < 0.0002$*	F = 46.8 $P < 0.0002$*

The coefficients of the third order polynomial functions fitted to the values for mouth opening in each experimental animal. The standardized coefficients of the two relaxant groups were compared by MANOVA (F = 15.8; $P < 0.001$) and ANOVA (*Bonferroni corrected). Values are expressed as mean ± SD.

rants further evaluation as a model for studying the responses of human jaw muscle to succinylcholine.

References

1. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effects of succinylcholine on mouth opening. Anesthesiology 1987;67:459–65.
2. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. Increased masticatory muscle stiffness during limb muscle flaccidity associated with succinylcholine administration. Anesthesiology 1988;69:11–6.
3. Herbert DA, Mitchell RA. Blood gas tensions and acid-base balance in awake cats. J Appl Physiol 1971;30:434–6.
4. Baird WLM, Bowman WC, Kerr WJ. Some actions of ORG NC 45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 1982;54:375–84.
5. Marshall IG, Gibb AJ, Durant NN. Neuromuscular and vagal blocking actions of pancuronium bromide, its metabolites, and vecuronium bromide (ORG NC 45) and its potential metabolites in the anaesthetized cat. Br J Anaesth 1983;55:703–13.
6. Choi WW, Gergis SD, Sokol MD. Effects of succinylcholine chloride on the response of fast and slow muscle in the cat. Acta Anaesthesiol Scand 1984;28:516–20.
7. Leary NP, Ellis FR. Masseter Myotonia with suxamethonium. Br J Anaesth 1988;60:345.

Poststernotomy Neuralgia: A New Pain Syndrome

Ray J. Defalque, MD, and Joel J. Bromley, MD

DEFALQUE RJ, BROMLEY JJ. Poststernotomy neuralgia: a new pain syndrome. Anesth Analg 1989;69:81–2.

Fifty-four patients developed severe intercostal neuralgia a few weeks after sternotomy. Immediate relief afforded by parasternal nerve blocks confirmed that the pain derived from scar-entrapped neuromas of the anterior rami of the first 4–6 intercostal nerves in the upper (and mainly left) interchondral spaces after insertion of the sternal wires. Permanent relief (i.e., over 6 months) followed repeated bupivacaine blocks in 57.4% of the patients, phenol blocks in another 22.2%, and alcohol blocks in a remaining 9%. Treatment was successful in 87% of the patients.

Key Words: PAIN—post-sternotomy. SURGERY—cardiovascular.

Two pain syndromes after heart surgery have been described in the past decade: the postcardiotomy syndrome (1) and brachial plexopathy (2,3). Over the past 8 yr, we have seen 80 patients with a different pain pattern, which, to our knowledge, has not been reported. We present our findings in 54 patients whom we were able to observe for at least 6 months.

Symptomatology

The 54 patients were 43–71-yr-old men who had recently undergone coronary grafting; four had concurrent aortic valve replacement. Sixty-one percent of the grafts came from the left internal mammary artery. The pain started between 4 weeks and 4 months (average 6 weeks) after the operation. The patients described a constant, severe, sharp pain ("like a stabbing or twisting knife") with a definite burning component at one or both sternal borders. The pain radiated to the anterior, lateral, and, in 12 patients, to the posterior chest wall. Eighteen of the 34 patients with left sternal pain also complained of pain in the left upper arm. All felt that the pain was definitely aggravated by chest wall movements (cough, deep breathing) and, even more, by arm movements.

All patients were referred by cardiologists who had ruled out recurrent angina or a postcardiotomy syndrome after exercise electrocardiography (ECG), coronary vasodilators, and, in most cases, computer tomographic (CT) scan, scintigraphy, and ventriculogram. Discrete, exquisitely tender trigger points could be elicited in all patients by pressing with a dull point at the sternal margin of the upper interchondral spaces. The pressure reproduced the pain and its radiation. Those trigger points were found 1) at the left sternal border in 34 patients: at T2–4 in 27 patients and at T2–6 in seven others; 2) at the right sternal margin in seven patients; at T2–4 in five patients and at T2–6 in two others; 3) at both sternal borders in the 13 remaining patients: at T2–4 in eight patients and T2–6 in two patients.

Diagnosis

Each trigger point was located as the tip of a 15.9 mm 25-gauge needle was felt to enter a hard nodule (scar?) and simultaneously produced an intense pain. Each point was then injected twice at an interval of a few days with 3 mL bupivacaine 0.75% with epinephrine 1:200,000. These two blocks caused complete pain relief in all patients for at least 8 hr. This result, we believed, confirmed our clinical impression of chest wall pain. The diagnosis was explained to the patient and consent for treatment obtained.

Treatment

The treatment was started with bupivacaine blocks (3 mL bupivacaine 0.75% with epinephrine 1:200,000) that were repeated when and if the pain returned. If the pain persisted after four bupivacaine blocks,

---

Received from the Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, Alabama and the Department of Anesthesiology, Veterans Administration Medical Center, Birmingham, Alabama. Accepted for publication February 14, 1989.

Address correspondence to Ray J. Defalque, MD, Department of Anesthesiology, B'HAM VAMC, 700 S. 19th St., Birmingham, AL 35233.

©1989 by the International Anesthesia Research Society

phenol (2–3 mL 6% aqueous phenol) was injected. In patients in whom four phenol blocks failed to give prolonged relief, alcohol (1.5–2 mL absolute alcohol) was injected.

The treatment was considered a failure if the pain returned after the fourth alcohol block.

Results

Forty-eight of the 54 patients (87%) were permanently relieved of pain, (i.e., relief for at least 6 months) after bupivacaine or neurolytic block: 1) Thirty-one patients had permanent relief from two to four bupivacaine blocks; 2) Neurolytic injections were successful in another 17 patients—twelve patients had two to four phenol blocks and five had one alcohol block; 3) The blocks failed in seven patients. With all neurolytic and with most therapeutic bupivacaine blocks, IV fentanyl (200–250 μg) was also given.

Complications

Probing the interchondral space, even with short needles, after a sternotomy is not innocuous as lung tissue may adhere to the anterior chest wall. Two of the 80 patients we treated developed a left pneumothorax, one severe enough to require a chest tube. Those two patients could not be observed for 6 months and therefore are not included in the 54 patients discussed here. There were no other complications, including alcohol or phenol neuritis.

Discussion

The exquisitely tender and hard nodules and the immediate and complete pain relief after the bupivacaine injections suggest that the pain these patients suffered from was caused by scar-entrapped neuromas of small terminal rami of the anterior branches of the upper intercostal nerves.

Such neuromas could result from the section (terminal neuromas) or damage (neuromas-in-continuity) of the nerve rami by the sternal wires or the needles inserted at the sternal margin of the interchondral spaces. It is likely that those tight sternal wires induced a marked scar reaction.

Such small scar-entrapped neuromas are extremely painful but respond well to the injection of small amounts of neurolytics (4). We attribute the high success rate of the blocks to the small diameter of the involved nerve rami. Our neurolytics were injected at the site of the trigger points and a true intercostal block was not performed. Intercostal blocks with most neurolytics, in our experience, only give short relief and, not uncommonly, a painful neuritis.

It is unclear to us and to our surgical consultants why the trigger points mainly occur in the left upper interspaces. However, the wires were generally tied on the left. That all our patients were men probably reflects the considerable preponderance of men undergoing coronary surgery in our surgical program at the time rather than the propensity of one gender to produce painful scar neuromas. Our other series of scar-entrapped neuromas (4) showed an equal ratio of patients of both genders.

Blocking the trigger points, especially with a neurolytic, is itself very painful. Our patients received no analgesic for their diagnostic blocks to avoid confusing the diagnosis, but incremental IV doses of up to 200–250 μg fentanyl were used when therapeutic blocks were carried out. This procedure produced short but intense analgesia without impairing the patients' ability to locate their trigger points. The pain caused by a neurolytic (especially phenol) lasts only a few minutes.

Although this syndrome has not been previously reported, poststernotomy parasternal trigger points were known to several dolorologists and surgeons with whom we discussed our patients. Some had treated them with repeated bupivacaine injections with or without steroids. We hope that this article will encourage others to report their experience with what probably is a common complaint. Its prevalence, the importance of its correct diagnosis, and its high rate of relief with simple measures recommend it to the physician's attention.

We thank Edward A. Ernst, MD and Judy McDanal, MD for helpful comments and suggestions. Part of this work was presented at the Second International Symposium of Regional Anesthesia, Williamsburg, VA, May 1988.

References

1. Winzelberg GG, Boller M. Chest pain following aortocoronary by-pass graft. JAMA 1982;248:1889–90.
2. Vander Salm TJ, Cutler MBS, Okike ON. Brachial plexus injury following median sternotomy. Part II. J Thorac Cardiovasc Surg 1982;83:914–7.
3. Hanson MR, Breuer AC, Furlan AJ, et al. Mechanism and frequency of brachial plexus injury in open heart surgery: a prospective analysis. Ann Thorac Surg 1983;36:675–9.
4. Defalque RJ. Painful trigger points in surgical scars. Anesth Analg 1982;61:518–20.

Humidity of the Bain and Circle Systems Reassessed

Jan P. Bengtson, MD, PhD, Anders Bengtson, MD, PhD, Hans Sonander, MD, PhD, and Ola Stenqvist, MD, PhD

BENGTSON JP, BENGTSON A, SONANDER H, STENQVIST O. Humidity of the Bain and circle systems reassessed. Anesth Analg 1989;69:83–6.

The humidity outputs of the Bain circuit, a traditional non-coaxial Mapleson D system, and a circle system with and without a soda lime absorber were evaluated in a laboratory model simulating a 70-kg subject. The breathing systems were tested with tidal volumes of 0.35 and 0.70 L and frequencies of 10–20 breaths/min to maintain an end-expiratory CO_2 *of 4.5%. There were small differences in inspiratory gas humidity between the Bain and the non-coaxial Mapleson D system. With a fresh gas flow of 5 L/min in the Bain circuit, the humidity was 9.8–16.5 mg* H_2O/L *depending on tidal volume and respiratory frequency. The humidity output of the circle absorber system with fresh gas flows of 0.5 or 2 L/min was 21.6–25.2 mg* H_2O/L *at 60 min. Therefore, this study does not support previous studies, which propose that the Bain circuit has superior humidifying properties compared with those of the circle absorber system.*

Key Words: EQUIPMENT, ANESTHESIA CIRCUITS—Bain, circle. ANESTHETIC TECHNIQUES—closed circuit systems.

Humidification of anesthetic gases has been recommended for the prevention of pulmonary damage and for maintenance of body temperature (1–5). Heat moisture exchangers (HME) and cascade hot water humidifiers for anesthesia circuits are available. Some anesthetic breathing systems, such as the circle absorber system and the Mapleson D system, have inherent humidifying properties.

In two different studies (6,7), the Bain circuit, a coaxial system of the Mapleson D classification, has been found to provide superior inspiratory gas humidity when compared with that of a circle absorber system. However, the introduction of circle systems with disposable small absorption canisters has greatly improved inspiratory gas humidification (8).

In the Bain circuit, there is only one source of water vapor, the rebreathing of exhaled gas. In the circle absorber system, there are two sources of water, rebreathing of exhaled gas and release from the soda lime. In an exothermic reaction, 2 mol of water and 14 kilocalories are liberated for each mole of carbon dioxide absorbed. Further, the circle absorber system permits a much lower rate of delivery of dry fresh gas. From a theoretical standpoint, one, therefore, would expect results other than those of the previously mentioned studies.

The aim of this laboratory investigation was to study inspiratory gas humidity of the Bain circuit, a traditional non-coaxial Mapleson D system, and a circle system with or without a soda lime absorber.

Methods

A Bennett cascade humidifier acted as a heat and moisture source in a lung model (Figure 1). Expiratory gas temperature in the core of the model was kept at 37°C by a separate thermostat. To simulate a subject with a weight of about 70 kg, 200 mL of carbon dioxide/min was added to the model. Expiratory gas volumes were measured with a Bourns Adult Ventilation Monitor LS-80 (Bourns Medical Systems Inc., Riverside, CA). At the "mouth" end of the model, a mini-circle separated inspiratory and expiratory gases (8).

Relative humidity (RH) and temperature of inspired gases were measured with a Vaisala HMI 32 (Vaisala OY, Helsinki, Finland) every 10 min until a steady state was reached. This device has a humidity sensor that operates on a capacitive principle. The stated system accuracy is ±3% RH and ±0.3°C. From

---

Received from the Department of Anesthesia and Intensive Care, Sahlgren Hospital, University of Göteborg, Göteborg, Sweden. Accepted for publication February 24, 1989.

Address correspondence to Dr. Bengtson, Department of Anesthesia and Intensive Care, Sahlgren Hospital, S-413 45, Göteborg, Sweden.

©1989 by the International Anesthesia Research Society

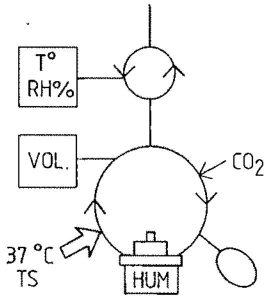


Figure 1. Lung model. A Bennett cascade humidifier (HUM) was controlled by a separate thermostat (TS) set at 37°C. A volume meter (VOL.) measured expired gas volumes. Inspiratory gas temperature (T°) and relative humidity (RH%) were measured with a Vaisala HMI 32 in a mini-circle. The breathing system tested was connected to the lung model above the mini-circle.

Table 1. Absolute Inspiratory Gas Humidity (mg H_2O/L gas) at 60 min With Tidal Volumes of 0.35 and 0.70 L in Different Breathing Systems

	Tidal Volume (L)	0.35	0.70
Breathing System	Fresh Gas Flow (L/min)	Absolute Humidity (mg H_2O/L)	
Bain	5	9.8	11.5
	7	6.5	6.5
	10.5	4.4	3.6
Mapleson D	5	7.9	9.7
	7	5.2	7.3
	10.5	4.3	3.2
Circle without absorber	5	6.8	9.9
	7	4.8	7.1
Circle with absorber	0.5	24.2	24.6
	2	23.3	23.4
	5	10.6	12.3

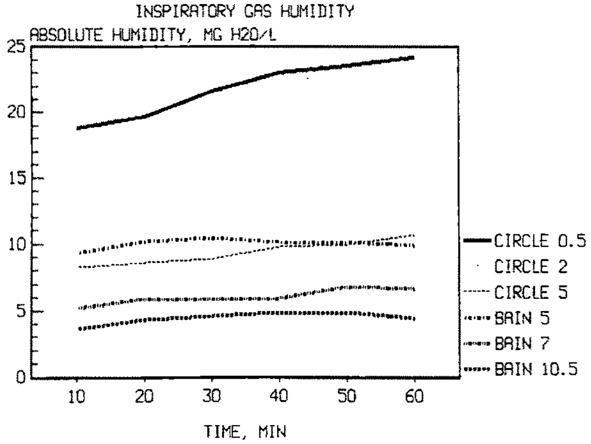


Figure 2. Inspiratory gas absolute humidity in milligrams of water per liter gas as a function of time with a respiratory frequency of 20 breaths/min and a tidal volume of 0.35 L. The fresh gas flows to the circle absorber system were 0.5, 2, and 5 L/min and to the Bain system 5, 7, and 10.5 L/min.

the mean inspired RH and temperature values, absolute humidity was calculated in milligrams of water per liter gas. Ambient temperature was measured with a Exacon Thermometer MC 8700 (Exacon, Copenhagen, Denmark). Because this temperature was relatively constant during the entire investigation, 23.6 ± 1.3°C, no corrections have been made of the inspiratory gas temperature values. Air with a relative humidity of <5% RH was used in all the experiments.

End-expiratory carbon dioxide was measured with a Datex Normocap (Datex Instrumentation, Helsinki, Finland). This monitor was calibrated before each experiment with certified calibration gas containing 3.0% carbon dioxide (2.99 ± 0.06%).

Four different breathing systems were used: a Bain circuit, a traditional non-coaxial Mapleson D system, a circle absorber system (Anmedic, Vallentuna, Sweden) with or without a 0.9 L disposable soda lime absorption canister. Silicone rubber tubing with a length of 1.1 m of each limb was used in the circle system experiments. The total volume of the circle system with the bellows in the full position was 3.3 L.

In a first set of experiments, the breathing systems were ventilated with a frequency of 10 breaths/min with a tidal volume of 0.70 L or a frequency of 20 breaths/min and a tidal volume of 0.35 L. Fresh gas flows of 5, 7, and 10.5 L/min were used for the Bain and Mapleson D systems, corresponding to 70, 100, and 150 ml·kg·min (9,10) and 0.5, 2, and 5 L/min for the circle absorber system. In the circle system without an absorber, the fresh gas flows were 5 and 7 L/min.

In a second experiment series, the breathing systems were ventilated with 10 or 20 breaths/min. The tidal volumes were adjusted to maintain an end-expiratory carbon dioxide concentration of 4.5%. The fresh gas flows were the same as those in the first experiment series.

Results

At 60 min, inspiratory gas absolute humidity was at steady state in the Bain, Mapleson D, and circle system without an absorber. The humidities were close to steady state in the circle absorber system. At 120 min, the absolute humidity values were within 10% of the values at 60 min. Regardless of breathing system tested, the inspired humidity was inversely proportional to the fresh gas flow. The inspiratory gas humidity of the Bain system tended to be higher than that in the non-coaxial Mapleson D system. However, the differences were never >2 mg H_2O/L. With a fresh gas flow of 5 L/min to the Bain system, the humidity was about 10 mg H_2O/L and 11.5 mg H_2O/L with tidal volumes of 0.35 and 0.70 L respectively (Table 1).

The inspired humidities of the circle absorber system were 10.6, 23.3, and 24.2 mg H_2O/L with fresh gas flows of 5, 2, and 0.5 L/min, respectively, when a

Table 2. Absolute Inspiratory Gas Humidity (mg H_2O/L gas) at 60 min With Tidal Volumes Causing an End-Tidal Carbon Dioxide Concentration of 4.5%

		20 Breaths/Min		10 Breaths/Min	
Breathing System	Fresh Gas Flow (L/min)	Tidal Volume (L)	Absolute Humidity (mg H_2O/L)	Tidal Volume (L)	Absolute Humidity (mg H_2O/L)
Bain	5	0.70	16.5	0.75	11.8
	7	0.55	14.3	0.65	9.6
	10.5	0.45	6.8	0.60	3.6
Mapleson D	5	0.70	18.6	0.75	11.9
	7	0.55	12.4	0.65	6.7
	10.5	0.45	7.1	0.60	3.7
Circle without absorber	5	0.55	13.7	0.65	11.0
	7	0.45	8.0	0.60	8.1
Circle with absorber	0.5	0.40	24.3	0.55	25.2
	2	0.40	24.3	0.55	21.6
	5	0.40	14.4	0.55	11.3

tidal volume of 0.35 L was used. Somewhat greater humidities were attained with a tidal volume of 0.70 L. The inspired humidities as a function of time of the circle absorber system and the Bain system are shown in Figure 2.

In the second experiment series with equal end-tidal CO_2 at frequencies of 10 and 20 breaths/min, there were again small humidity differences between the Bain and the non-coaxial Mapleson D systems (Table 2). The circle system without an absorber required smaller tidal volumes than those of the Bain and Mapleson D systems to maintain end-tidal CO_2 at 4.5%, when tested with the same fresh gas flow. The inspired humidity in the circle system without absorber was a little lower with a maximum 13.7 mg H_2O/L with a fresh gas flow of 5 L/min and a respiratory frequency of 20 breaths/min. The humidities of the circle absorber system ranged from 11.3 to 25.2 mg H_2O/L depending on fresh gas flow and respiratory frequency.

Discussion

Both under- and over-humidification may have negative effects on pulmonary function. Optimal levels of inspired humidification during artificial ventilation are probably between 17 and 33 mg H_2O/L (1–3,11,12).

The inspired humidity levels are dependent on fresh gas flow in both the circle system and the Bain system. The greater the fresh gas flow, the lower the humidity. With fresh gas flows of 0.5–5 L/min to the circle absorber system, the inspired humidity ranged from 10.6 to 25.2 mg H_2O/L at 60 min. Corresponding humidity range of the Bain system was 3.6–16.5 mg H_2O/L with fresh gas flows of 5–10.5 L/min.

The results of this study are in contrast to the studies by Rayburn and Watson (7) and Ramanathan et al. (6). In the former study, humidities of normocapnic children anesthetized with a Bain system were constant between 24 and 26 mg H_2O/L after 30 min. The circle system with a fresh gas flow of 5 L/min gave a humidification of 10 mg H_2O/L, whereas a closed circle system in adults yielded 13 mg H_2O/L at 30 min to 19 mg H_2O/L at 2 hr. The humidity sensor was placed in the inspiratory limb of the circle system and between the breathing circuit and the endotracheal tube of the Bain circuit. However, in the latter situation, expiratory gas humidity interferes with the inspiratory measurements. This result is due to a relatively long response time of commonly used hygrometers (13). During expiration, warm and saturated gas condensate on the humidity sensor, resulting in increased temperature and hysteresis in displayed humidity during the subsequent inspiration. This interference is not a problem in the circle system if the humidity sensor is placed in the inspiratory limb. In our study a mini-circle separated inspiratory and expiratory gases, thereby eliminating this error and permitting a comparison between the Bain and circle absorber system humidities.

Ramanathan et al. (6) tested humidity output and CO_2 elimination of the Bain circuit in a simulated 70-kg patient. The initial humidity output of the Bain circuit was 14 mg H_2O/L with a stabilization at 21 mg H_2O/L after 70 min of use. They used a fresh gas flow of 4.9 L/min. This fresh gas flow used with a minute ventilation of 8.4 L/min resulted in a F_{ICO_2} of 0.024. However, to avoid excessive rebreathing with elevated inspiratory gas carbon dioxide concentration, they did "strongly recommend that fresh-gas flow always be maintained at 8 L/min to cover all eventualities." They did not present data on humidity levels with the recommended fresh gas flow. Most likely, a higher fresh gas flow would result in a lower inspiratory gas humidity. In their circle system experiments, the humidity output was initially 6 mg H_2O/L, progressively increasing to 13 mg/L at 80 min. The fresh gas flow was 5 L/min.

The humidity output of the Bain circuit with a fresh gas flow of 5 L/min in this study was 9.8–16.5 mg H_2O/L, depending on tidal volume and respiratory frequency. These findings are in agreement with a clinical study by Weeks (11), who found wide variations in inspiratory gas humidity from the Bain circuit. The mean values in Weeks' study were 12–13.5 mg H_2O/L when the fresh gas flow was 70 ml·kg·min or 5 L/min, whichever was greater.

The coaxial construction of the Mapleson D circuit did not greatly improve humidification in the present study. Therefore, the temperature counter current mechanism is probably of little importance. Somewhat surprisingly, the circle system without absorber was almost as good as a humidifier and even more effective in carbon dioxide elimination at equal fresh gas flows.

The circle absorber system permits fresh gas flows corresponding to the patient's gas uptake rates, i.e., closed circuit anesthesia. However, for safety and simplicity, fresh gas flows of 3–5 L/min have been used. In the past few years, technical developments including oxygen analyzers and more precise flowmeters have contributed to a repopularization of low flow techniques.

In conclusion, the present study demonstrated an adequate humidification with fresh gas flows of 0.5 and 2 L/min when a small volume circle system with a plastic absorption canister was used. The Bain system did not meet optimal humidification requirements, regardless of fresh gas flow used.

References

1. Ingelstedt S. Studies on the conditioning of air in the respiratory tract. Acta Otolaryngol 1956;(suppl 131):1–80.
2. Tsuda T, Noguchi H, Takumi Y, Aochi O. Optimum humidification of air administered to a tracheostomy in dogs. Br J Anaesth 1977;49:965–76.
3. Forbes AR. Temperature, humidity and mucus flow in the intubated trachea. Br J Anaesth 1974;46:29–34.
4. Stone DR, Downs JB, Paul WL, Perkins HM. Adult body temperature and heated humidification of anesthetic gases during general anesthesia. Anesth Analg 1981;60:736–41.
5. Tollofsrud SG, Gundersen Y, Andersen R. Peroperative hypothemia. Acta Anaesthesiol Scand 1984;28:511–5.
6. Ramanathan S, Chalon J, Capan L, Patel C, Turndorf H. Rebreathing characteristics of the Bain anesthesia circuit. Anesth Analg 1977;56:822–5.
7. Rayburn RL, Watson RL. Humidity in children and adults using the controlled partial rebreathing anesthesia method. Anesthesiology 1980;52:291–5.
8. Bengtson JP, Sonander H, Stenqvist O. Preservation of humidity and heat of respiratory gases during anaesthesia. Acta Anaesthesiol Scand 1987;31:127–31.
9. Bain JA, Spoerel WE. Flow requirements for a modified Mapleson D system during controlled ventilation. Can Anaesth Soc J 1973;20:629–36.
10. Jonsson LO, Johansson LG, Zetterström H. Rebreathing and ventilatory response to different fresh gas flows in the Bain and Lack systems. A clinical study. Acta Anaesthesiol Scand 1987; 31:179–86.
11. Weeks DB. Provision of endogenous and exogenous humidity for the Bain breathing circuit. Can Anaesth Soc J 1976; 23:185–90.
12. Shelly MP, Lloyd GM, Park GR. A review of the mechanisms and methods of humidification of inspired gases. Intensive Care Med 1988;14:1–9.
13. Carr-Brion K. Moisture Sensors in Process Control. London: Elsevier Science Publishing, 1986:4–28.

Acute Acid Aspiration Lung Injury in the Rat: Biphasic Pathogenesis

Thomas P. Kennedy, MD, Kent J. Johnson, MD, Robin G. Kunkel, BS, MA,
Peter A. Ward, MD, Paul R. Knight, MD, PhD, and Jay S. Finch, MD

KENNEDY TP, JOHNSON KJ, KUNKEL RG, WARD PA, KNIGHT PR, FINCH JS. Acute acid aspiration lung injury in the rat: biphasic pathogenesis. Anesth Analg 1989;69:87–92.

The purpose of this study was to develop a reproducible model of acute acid aspiration-induced lung injury in the rat to explore the pathophysiology of aspiration pneumonitis. A biphasic injury pattern was observed with injury peaks at 1 hr and 4 hr. Histologic studies at 4 hr revealed significant increases in neutrophils in the alveolar interstitial space. These studies suggest that acid aspiration results in a biphasic acute injury. We hypothesize that the first phase results from a direct physiochemical process or is mediated via afferent (capsaicin sensitive) nerves or both. The second phase, occurring 2–3 hr later, is mediated by neutrophils and is consistent with an acute inflammatory response.

Key Words: COMPLICATIONS, ASPIRATION. LUNG, ASPIRATION.

Ever since Simpson (1) discussed the first reported anesthetic related death in 1848, aspiration has been an ever present concern to the anesthesiologist. It has been reported to be the cause of up to 20% of all anesthetic-related deaths (2). In patients who aspirate gastric contents, the mortality rate averages 30%, and it is a leading cause of maternal mortality during obstetric anesthesia (3,4).

Since Mendelson (5) first described the syndrome of gastric aspiration followed by acute pneumonitis over 40 years ago, several animal models of aspiration pneumonitis have been described in the literature. None, however, have addressed all of the variables necessary for the development of maximal acute *nonlethal* lung injury. The pH and volume of the solution aspirated are the major determinants of the degree of lung injury associated with aspiration of gastric contents (6). Studies have examined the effect of single variables, for example, the effect of pH (7–9) and volume (10). Yet there are only two studies reported that have examined both pH and volume together in the same animal model and their measure of injury was death. Most authors agree that a pH of <2.5 and a volume of gastric aspirate >20–25 ml in the adult are the critical values in the development of aspiration pneumonitis (6). Although experimental studies on the effect of pH are well documented, they are based on lethality and have not quantified the injury in the more acidic range. The conclusions regarding critical volume are based on limited studies done on rhesus monkeys (11). Finally, no studies have systematically examined the time course of the acute acid aspiration injury.

To further examine the pathophysiology of aspiration pneumonitis, first it is necessary to define the conditions associated with maximal acute nonlethal lung injury. Thus, the purpose of this study was to define the conditions of maximal nonlethal lung injury associated with acid aspiration in rats. This study has for the first time looked at the effect of pH, volume, and time as well as providing a morphologic evaluation of the acute *nonlethal* lung injury using an animal model with aspiration of clear liquids. Definition of the conditions associated with maximal lung injury in this syndrome as outlined in "Methods" is of value in increasing our understanding of the sequence of events that occurs in humans, as well as providing clues on the mediation of this type of injury.

Received from the Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor, Michigan.

This work was supported in part by an Anesthesiology Fellowship Award from Stuart Pharmaceuticals, Wilmington, Delaware. Accepted for publication February 20, 1989.

Address correspondence to Dr. Kennedy, Department of Anesthesiology, Clinical Faculty Office Building, Box 0704, University of Michigan Medical Center, Ann Arbor, MI 48109.

©1989 by the International Anesthesia Research Society

Methods

The following methods were approved by the University of Michigan Committee on Use of and Care of Animals.

Animal Model

Male pathogen-free Long-Evans rats weighing between 300 and 350 g were used in these studies (Charles River, Portage, MI). The rats were anesthetized with intraperitoneal ketamine 1 mg/kg of body weight. The trachea of each rat was exposed surgically and a 16-gauge needle was inserted through tracheal cartilage. A catheter was then advanced through the needle until it was just above the carina and then the experimental solution was injected. The hydrochloric acid solution (HCl) was reagent grade and the stock solution of acid was diluted to the desired pH by the addition of sterile normal saline. After instillation of the acid solution (or sterile normal saline in control animals) the needle and catheter were withdrawn and the tracheostomy incision was closed with silk sutures. The animals generally recovered within 30 min from the effects of the anesthetic and operative procedure and were then put into individual clean cages with water ad lib for the duration of the experiment. At the times described in the next paragraph, the animals were sacrificed and the intensity of the lung injury was quantitated.

Quantitation of Lung Injury

Pulmonary injury was quantitated by permeability measurements as well as by morphologic studies. Permeability studies were done by measuring the leakage of radiolabeled protein (^{125}I-albumin) from the circulation into the lung. The radiolabeled protein was injected intravenously at the same time as the acid was instilled into the lungs. The animals were sacrificed by an intraperitoneal injection of ketamine followed by transection of the vena cava. Exactly 1 ml of blood was collected from the inferior vena cava and counted for radioactivity. The heart and lungs were then removed as a whole and 10 mL of sterile saline was infused into the right ventricle to remove blood (and radioactivity) from the pulmonary circulation. The lungs were then isolated and the radiolabeled albumin was counted in a gamma crystal scintillation counter. The radioactivity remaining in the lung was a measure of vascular permeability and this was compared to 1 mL of the same animal's blood. Therefore, each animal functioned as its own control in terms of total radioactivity injected, and a ratio of lung radioactivity to blood radioactivity was calculated giving a quantitative measurement of lung injury known as the permeability index (PI). Our laboratories, as well as others (12,13,14), have had considerable experience with this method and have found that the degree of change in permeability correlates well with the degree of lung injury as assessed by histologic criteria. Table 1 summarizes the conditions and the number of animals used to generate the permeability data.

Table 1. Conditions and Number of Animals Used to Generate Permeability Data

	pH	No. of Animals
pH studies	1.5	8
	1.8	5
Volume = 1.2 mL/kg	2.5	5
Sacrificed 4 hr after injury	3.0	6
	Saline (control)	4
	mL/kg	No. of Animals
Volume studies	0.5	5
	1.0	6
pH = 1.5	1.2	5
Sacrificed 4 hr after injury	2.0	6
	Saline (control)	4
	Time (hr)	No. of Animals
Time studies	1	7
	2	6
pH = 1.5	3	5
Volume = 1.2 mL/kg	4	8
	6	6
	15	5
	Saline (control)	4

Histologic studies were also performed to further describe and quantitate the injury. The lungs were processed with use of constant pressure glutaraldehyde fixative inflation of the lungs (25 cm H_2O). Sections of lung tissue were then processed for transmission electron microscopy (TEM) and light microscopy with use of routine procedures. TEM generated qualitative information, whereas light microscopy slides were used to generate quantitative information from morphometric analysis.

Morphometric analysis was also performed in four groups of animals: a control group and three experimental groups with each individual group consisting of two–four animals. The experimental groups were injured with a solution of HCl at a pH of 1.5 and volume equal to 1.2 mL/kg and then sacrificed at 1 hr (group 1), 4 hr (group 2), and 15 hr (group 3). Light microscopy sections were prepared and at least 40 high powered fields containing interstitial capillaries and alveoli were randomly selected for analysis. The

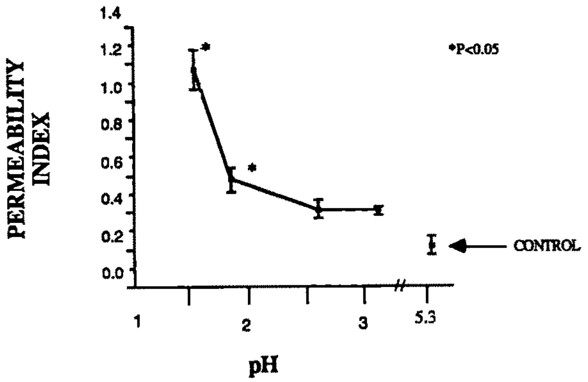


Figure 1. The pH response curve demonstrates changes in lung permeability index (PI) related to changes in pH of hydrochloric acid aspirate. Maximal nonlethal lung injury occurs at pH 1.5. Volume of aspirate was 1.2 mL/kg; animals were killed and PI determined 4 hr after intratracheal injection of the test solution. Each data point represents at least 5 animals. Statistical significance was determined with use of ANOVA and the Scheffe f test. *Values significantly different from those of controls (normal saline pH = 5.3, volume 1.2 mL/kg).

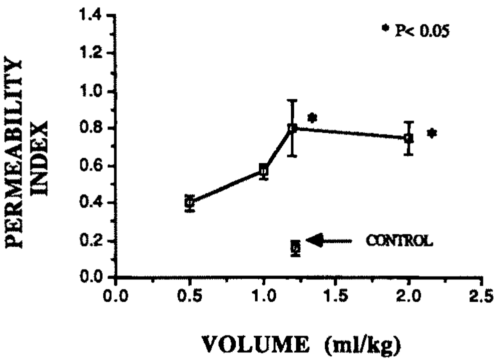


Figure 2. Volume response curve represents changes in lung permeability index (PI) related to changes in volume of aspirated acid. pH of the solution was 1.5; animals were killed and PI determined 4 hr after intratracheal injection of test solution. Maximal nonlethal lung injury occurred at volume of 1.2 mL/kg. Each data point represents at least 5 animals. Statistical significance was determined with use of ANOVA and the Scheffe f test. *Values significantly different from those of controls (normal saline pH = 5.3 volume 1.2 mL/kg).

number of polymorphonuclear cells (PMNs) per high powered field (HPF) and the number of intra-alveolar red blood cells (RBCs) per HPF were determined.

To evaluate the statistical significance of the data, tests for multiple comparison were used: these were analysis of variance (ANOVA) and the Scheffe f test. Values are expressed as mean ± SEM. Statistical significance was accepted at the 5% level ($P < 0.05$).

Results

Effect of pH

As illustrated in Figure 1, at a pH of 1.5, there was a significant increase in lung permeability as compared with controls (pH 5.3) (0.97 ± 0.24 vs 0.17 ± 0.43). At lower pH values, the instillation of the acid solutions was lethal, whereas at higher pH values the degree of lung injury decreased. At a pH of 1.8, the PI was significantly greater than that of the negative controls (0.50 ± 0.16 vs 0.17 ± 0.43). At a pH of ≥2.5, the degree of lung injury tended to plateau at levels around twofold greater than those of control animals.

Effect of Volume

The results of the volume studies are shown in Figure 2. At a volume of 0.5 mL/kg, the mean PI was 0.40 ± 0.09; when the volume of the aspirate increased to 1.2 mL/kg the lung injury was increased significantly, almost twofold (PI of 0.80 ± 0.34; $P < 0.05$). This linear relationship was lost at higher volumes, there being no significant increase in the degree of injury observed with volumes >1.2 mL/kg. At 2 mL/kg, the degree of lung injury was about the same as that seen when 1.2 mL/kg was used (0.79 ± 0.23).

Time Course of the Lung Injury

There was an initial early peak of injury 60 min after acid aspiration, with mean PI values of 0.47 ± .09 vs 0.17 ± 0.04 for control animals, ($P < 0.05$) (Figure 3). The PI values at 2 and 3 hr were nearly the same as those at 1 hr. Four hours after the instillation of the acid, however, the PI values increased significantly to 0.97 ± 0.24. The degree of injury remained high at 6 hr with mean values of 0.93 ± 0.27. By 15 hr, however, the injury appeared to be diminishing with a mean PI value that had decreased to 0.21 ± 0.07, not statistically different from the control values.

Morphology

The composite photograph in Figure 4A represents a lung section from a control rat (normal saline aspirate). Alveoli are clear and blood vessels are free of damage. By comparison, the other pictures represent sections taken from injured animals (pH 1.5, volume 1.2 mL/kg, 4 hr after injury). Figure 4B shows intra-alveolar RBCs and endothelial cell damage as evidenced by elevated basement membrane. Photomicrographs 4C and 4D illustrate an acute inflammatory response with recruitment of neutrophils and the formation of fibrin.

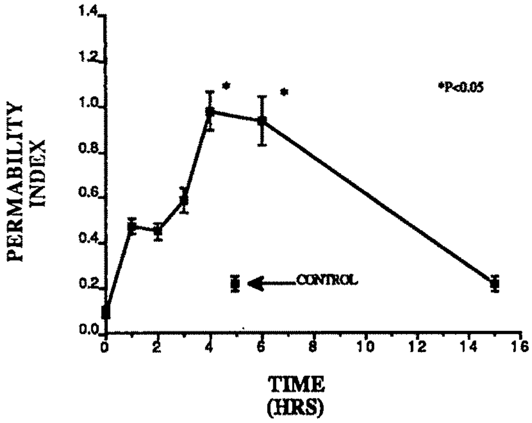


Figure 3. Time response curve represents changes in lung permeability index (PI) over time after intratracheal lung injection of 1.2 mL pH 1.5 solution. Initial injury measured after 1 hr demonstrated PI doubling when compared with control (normal saline pH = 5.3, volume = 1.2 mL/kg). By 4 hr, injury peaked. Volume of aspirate was 1.2 mL/kg; the pH of hydrochloric acid was 1.5. Each data point represents at least 5 animals. Statistical significance was determined with use of ANOVA and Scheffe f test. *Values significantly different from those of controls.

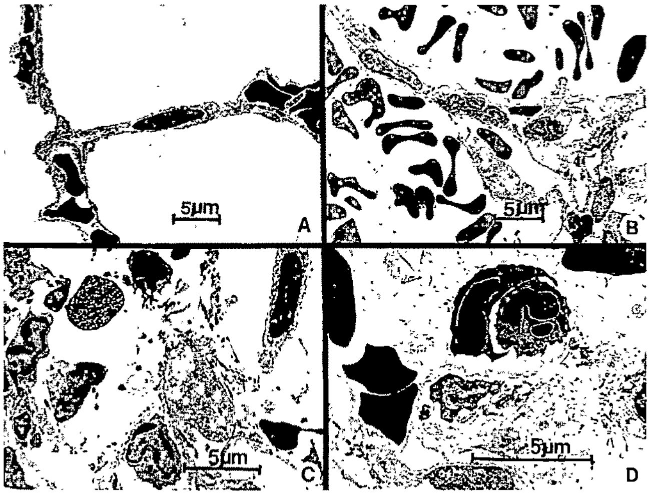


Figure 4. Morphologic changes 4 hr after intratracheal injection of various solutions. **A** shows absence of injury to lungs of control animals given pH 5.3, 1.2 mL/kg of normal saline (transmission electron microscopy [TEM] × 2811). **B–D** represent appearances of lung injured by the instillation of pH 1.5, 1.2 ml hydrochloric acid. In **B**, there are neutrophils in alveolar capillaries, damage to alveolar endothelial cells, and edema with intra-alveolar hemorrhage (TEM × 2824). **D** shows areas of intense acute injury with destruction of alveolar capillary walls and necrosis of lung parenchymal cells; many neutrophils are also present along with fibrin deposition and erythrocytes (TEM × 7419).

We examined the lung interstitial capillary and alveolar compartments and quantitated the number of neutrophils per high powered field and the number of intra-alveolar erythrocytes per high powered field; (Table 2). At 1 hr there was no significant change from control value for PMNs/HPF or intra-alveolar RBCs. By 4 hr there was a marked influx of inflammatory cells with the number of PMNs/HPF almost doubling. The number of intra-alveolar erythrocytes follows the same pattern with a doubling of the number of erythrocytes in the alveolar compartments (control 10.58 ± 0.33; 1 hr 15.23 ± 2.71 and 4 hr 32.82 ± 4.04). By 15 hr, when the permeability measurements had returned to baseline, both the number of PMNs/HPF and intra-alveolar erythrocytes had also returned to control values (15 hr PMNs 5.18 ± 0.35 and intra-alveolar erythrocytes 15.39 ± 1.44).

Table 2. Morphometric Analysis of Acid Aspiration-Induced Lung Injury After Intratracheal Instillation of Hydrochloric Acid* vs Normal Saline Controls

Time	No. of Sections	Neutrophils/HPF‡	Intra-alveolar Erythrocytes/HPF
Saline controls	50	4.44 ± 0.53	10.58 ± 1.33
1 hr	40	3.95 ± 0.62	15.23 ± 2.71
4 hr	65	7.1 ± 0.76†	32.82 ± 4.04†
15 hr	100	5.18 ± 0.35	15.39 ± 1.44

*pH 1.5; volume 1.2 mL/kg.
†$P < 0.05$ compared with control by ANOVA (Scheffe f test corrected).
‡HPF = high powered field.

Discussion

To further understand the pathophysiology of acid aspiration and investigate possible therapeutic interventions, it is first important to develop and characterize an animal model in which to examine pathophysiological processes. Furthermore, by defining the conditions (pH, volume, and time course) for maximal lung injury, one can reduce the variability inherent in this model. Under the conditions of the present study, maximal nonlethal injury occurred after aspiration when the pH of the aspirate was 1.5, the volume was 1.2 mL/kg, and 4 hr had elapsed since instillation of acid. With this information, one can begin to design experiments using interventions to determine conditions under which the degree of injury is lessened due to the intervention and not due to variability inherent in the model itself. For example, if one chose to design an experiment with this model using a pH of 1.65 (given the accuracy range of a pH meter), one might see large differences in injury based on small, unavoidable differences in the pH solution rather than on the specific intervention. Also, if the animals were killed at 3 hr instead of 4 hr, one might see a large variance based on the fact that at that time lung permeability is changing rapidly and the amount of injury may reflect the timing of the sacrifice, rather than that of the intervention. Therefore, with the knowledge we have of this model, we can now more accurately investigate mediators of pulmonary injury after gastric aspiration.

This series of experiments also further defines the relationship of pH and volume of aspirate to that of the degree of injury, as well as the chronology of the acute injury and our data are consistent with those of the study reported by James et al. (15). In their experimental design, the end point was death. They showed that the critical determinant of death after clear liquid aspiration was the pH of the solution. Their data suggest that in using volumes of aspirate <4 ml/kg, the critical pH is between 1.4 and 1.8. This range is consistent with our study. The pH response curve that we generated showed a significant increase in injury with a pH <1.8; with higher pH values the injury curve flattened out and approached control. However, it must be pointed out that at a pH of 2.5 the PI was still twice that of controls. In addition, with volumes of aspirate <1.2 mL/kg (at pH 1.5), there was a linear relationship between injury (PI) and volume of aspirate, but volumes >1.2 mL/kg did not cause greater injury. Therefore, we conclude (as did James and colleagues [15]) that the pH of the clear liquid solution aspirated is a more important determinant of lung injury than is volume.

Several studies (16,17) have demonstrated the association of gastric aspiration and the subsequent development of the adult respiratory distress syndrome (ARDS). Furthermore, there is evidence (18) that suggests that neutrophils are important mediators in the development of ARDS. Other investigators (19–20) have presented histologic evidence suggesting that the development of lung injury secondary to aspiration of HCl is mediated via inflammatory cells. As is demonstrated in our morphologic data, neutrophils, the key effector cells in acute inflammatory response, are present in significantly increased numbers in the test animals. In summary, the lung injury that develops in this model is at least partially mediated by neutrophils.

Furthermore, our data demonstrate that acid aspiration causes a biphasic injury pattern that has at least two different mechanisms of injury, as revealed in the histologic studies and the capillary permeability data. The histologic studies showed no significant change in the number of neutrophils at 1 hr despite evidence of marked capillary leakage. However, by 4 hr there is almost a doubling of the number of neutrophils in the lung and a similar additional increase in the capillary leakage (PI). We hypothesize that the initial increase in capillary permeability is analogous to a direct chemical burn or secondary to afferent (capsaicin sensitive) nerves (21). The second phase of the injury is an acute inflammatory response that reaches maximal levels 4 hr after acid aspiration. Clinically, this result suggests that there is a 2–3 hr window in which therapeutic manipulations of neutrophils and neutrophil function might be useful. Treatment during this time may decrease the morbidity and mortality associated with aspiration pneumonitis.

In summary, we have developed an animal model of aspiration pneumonitis in which we can measure nonlethal lung injury on a continuous scale. We have confirmed the importance of the pH of the aspirated solution as the critical determinant of the amount of injury. Our data suggest a biphasic injury pattern in acid aspiration pneumonitis mediated by different pathways. The initial mediators of this injury may be by afferent (capsaicin sensitive) (21) nerves, and this warrants further investigation. The second phase of the acute acid aspiration-induced injury is mediated, at least partially, by neutrophils and histologically mimics models of ARDS. Manipulations of possible mediators of this pathway of injury by such things as neutrophil and complement depletion warrant additional study and may add further insights into the pathophysiology of aspiration pneumonitis and possibly ARDS in general.

We would like to give special thanks to Bradley Nelson, BS, for expert assistance in preparing the histology sections.

References

1. Simpson JY. The alleged case of death from the action of chloroform. Lancet 1848;1:175–6.
2. Boadlander FMS. Deaths associated with anaesthesia. Br J Anaesth 1975;47:36–40.
3. Marx GF, Mateo CV, Orkin LR. Computer analysis of postanesthetic deaths. Anesthesiology 1973;39:54–8.
4. Cheek TG, Gutsch BB. Pulmonary aspiation of gastric contents. In: Shnider SM, Levinson G, eds. Anesthesia for Obstetrics. Baltimore: Williams & Wilkins, 1987:300–15.
5. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol 1946; 52:191–205.
6. Manchikanti L, Colliver JA, Marrero TC, Roush JR. Ranitidine and metoclopramide for prophylaxis of aspiration pneumonitis in elective surgery. Anesth Analg 1984;63:903–10.
7. Awe WC, Fletcher WS, Jacob SW. The pathophysiology of aspiration pneumonitis. Surgery 1966;60:232–9.
8. Teabeaut JR. Aspiration of gastric contents: an experimental study. Am J Pathol 1952;28:51–68.
9. Hamelberg W, Bosomwoth PP. Aspiration pneumonitis: experimental studies and clinical observations. Anesth Analg 1964;43:669–77.
10. Greenfield LJ, Singleton RP, McCaffree DR, Coalson JJ. Pulmonary effects of experimental graded aspiration of hydrochloric acid. Ann Surg 1969;170:74–86.

11. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. Anesth Analg 1974;53:859–68.

12. Johnson KJ, Wilson BS, Till GO, Ward PA. Acute lung injury in rat caused by immunoglobulin A immune complexes. J Clin Invest 1984;74:358–69.

13. Till GO, Beauchamp C, Menapace D, et al. Oxygen radical dependent lung damage following thermal injury of rat skin. J Trauma 1983;23:269–75.

14. Till GO, Johnson KJ, Kunkel R, Ward PA. Intravascular activation of complement and acute lung injury: dependency on neutrophils and toxic oxygen metabolites. J Clin Invest 1982; 69:1126–35.

15. James CF, Modell JH, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration-effects of volume and pH in the rat. Anesth Analg 1984;63:665–8.

16. Fowler AA, Humman RF, Good JT, et al. Adult respiratory distress syndrome: risk with common predispositions. Ann Intern Med 1983;98:593–7.

17. Pepe PE, Potkin RT, Reus DH, Hudson LD, Carrico CJ. Clinical predictors of the adult respiratory distress syndrome. Am J Surg 1982;144:124–30.

18. Ward PA, Johnson KJ, Till GO. Current concepts regarding adult respiratory distress syndrome. Ann Emerg Med 1985; 14:724–8.

19. Wynne JW. Aspiration pneumonitis: correlation of experimental models with clinical disease. Clin Chest Med 1982;3:25–34.

20. Manny J, Manny N, LeLuck S, et al. Pulmonary and systemic consequences of localized acid aspiration. Surg Gynecol Obstet 1986;162:259–67.

21. Claes-Roland M, Lundberg JM. Capsaicin sensitive afferents contribute to acute airway edema following tracheal instillation of hydrochloric acid or gastric juice in rat. Anesthesiology 1988;68:350–6.

ANESTH ANALG
1989;69:93–9

Comparison of Tracheal Intubating Conditions and Neuromuscular Blocking Profiles after Intubating Doses of Mivacurium Chloride or Succinylcholine in Surgical Outpatients

M. E. Goldberg, MD, G. E. Larijani, PharmD, S. S. Azad, MD, M. Sosis, MD, PhD, J. L. Seltzer, MD, J. Ascher, MD,* and J. N. Weakly, PhD*

GOLDBERG ME, LARIJANI GE, AZAD SS, SOSIS M, SELTZER JL, ASCHER J, WEAKLY JN. Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. Anesth Analg 1989;69:93–9.

Thirty ASA physical status I or II outpatients scheduled to undergo short procedures (<1 hr in duration) requiring tracheal intubation received either 1.0 mg/kg succinylcholine or 0.20 mg/kg (2.5 × ED_{95}) or 0.25 mg/kg (3 × ED_{95}) mivacurium. A N_2O/O_2/narcotic anesthetic technique was utilized and the ulnar nerve was stimulated with subcutaneous electrodes placed at the wrist. Tracheal intubation was attempted in all patients either 2 min after mivacurium or 1 min after succinylcholine. Intubation conditions were not different between the succinylcholine and mivacurium groups or between the two mivacurium groups. The onset and duration of neuromuscular blockade were shorter with succinylcholine than with mivacurium. Suppression of the T_1 response to 90% of baseline occurred in 0.9 min with 1.0 mg/kg succinylcholine and at 2.2 and 1.5 min respectively, with 0.20 mg/kg and 0.25 mg/kg mivacurium. Initial recovery of the T_1 response occurred at 6.4 min after 1.0 mg/kg succinylcholine and 12.7 and 13.6 min respectively after 0.20 mg/kg and 0.25 mg/kg mivacurium. Subsequent to initial recovery from the intubating dose of relaxant, infusions of mivacurium or succinylcholine were administered to maintain approximately 95% block. The mean infusion rates were 6.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ mivacurium and 41.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for succinylcholine. Spontaneous recovery from neuromuscular blockade occurred more quickly after succinylcholine than after mivacurium: the time from cessation of infusion to recovery of T_1 to 95% of baseline was 6.5 min in patients given succinylcholine and 16.7 min in patients given mivacurium. When reversal was in order, residual mivacurium-induced blockade was readily antagonized by 0.045 mg/kg neostigmine. In a small group (n = 7) of patients given mivacurium in whom neuromuscular function was still 77–99% blocked when neostigmine was given, the average time from administration of neostigmine to recovery of T_1 to 95% of baseline was 7.6 min. There were no differences in the duration of recovery room stay for patients receiving succinylcholine or mivacurium.

Key Words: NEUROMUSCULAR RELAXANTS, MIVACURIUM—succinylcholine. INTUBATION, TRACHEAL.

Mivacurium chloride is a new benzylisoquinolinium nondepolarizing neuromuscular blocking agent with a relatively rapid onset, but short duration of action (1–5). Initial studies (6–10) showed that the duration of action of mivacurium is approximately ½ to ⅓ that of equipotent doses of atracurium or vecuronium and twice that of conventional intubating doses of succinylcholine. There are many clinical situations in which the well-known side effects of succinylcholine make its use inappropriate or undesirable. Moreover, the duration of action of the intermediate-acting agents, atracurium and vecuronium, may be too long for some short procedures. Therefore, the availability of a short-acting nondepolarizing muscle relaxant may offer some advantages in the management of short surgical cases of the type commonly conducted in an outpatient setting. The purpose of this study was to evaluate and compare, in a blind fashion, the

---

Received from the Department of Anesthesiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania and *Division of Clinical Research, Burroughs Wellcome Company, Research Triangle Park, North Carolina 27709.

Presented in part at the Annual Meeting of the International Anesthesia Research Society, San Diego, California, March 1988. Accepted for publication February 20, 1989. Supported in part by a Grant from Burroughs Wellcome Company, Research Triangle Park, North Carolina 27709.

Address correspondence to Dr. Goldberg, Department of Anesthesiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107.

©1989 by the International Anesthesia Research Society

neuromuscular blocking profile and endotracheal intubating conditions associated with intubating doses of succinylcholine and mivacurium in outpatients undergoing brief procedures under N_2O/O_2/narcotic anesthesia. Two different doses of mivacurium, representing approximately 2.5–3 times the ED_{95} neuromuscular blocking dose (1), were selected for study. In addition, use of mivacurium or succinylcholine by continuous IV infusion for maintenance of block was compared.

Methods

Thirty ASA physical status I or II patients ranging in age from 22 to 63 years were studied after obtaining informed consent and institutional review board approval. All patients were scheduled for elective outpatient procedures requiring tracheal intubation and expected to be ≤1 hr in duration. Anesthesia was induced in each patient with thiopental, 4–6 mg/kg and fentanyl, 1.0–1.5 μg/kg and maintained with additional fentanyl as clinically indicated and 70% N_2O in O_2. Immediately after induction and loss of consciousness in the patient, the ulnar nerve was stimulated with a Digistem II nerve stimulator through subcutaneous electrodes placed at the wrist. Stimulation consisted of supramaximal train-of-four square wave impulses (0.2 msec duration at 2 Hz for 2 sec) every 12 sec. The mechanomyographic response of the adductor pollicis muscle was quantified with a Grass FT10 force transducer and recorded on a Gould polygraph. After establishment of a stable baseline twitch response, 20 patients (assigned on a random basis) were given 1.0 mg/kg succinylcholine or 0.25 mg/kg mivacurium over 10 sec through a rapidly running IV catheter. In the second part of the study, 0.20 mg/kg of mivacurium was similarly administered to ten patients. Suppression of the T_1 response (first response of the train-of-four) after administration of the muscle relaxant was expressed as a percentage of the baseline T_1 response before relaxant administration.

To maintain a normal end-tidal Pco_2 as measured by a Datex 254 (Puritan Bennett Corp.) infrared absorption monitor, ventilation was controlled with a face mask in place until intubation was accomplished. All intubations were attempted 2 min after administration of mivacurium or 1 min after succinylcholine and evaluated by an investigator blind to the neuromuscular blocking agent. This evaluation was accomplished by having the investigator immediately outside the room at the start of the case, who then approached and prepared the patient for intubation approximately 15 sec before the desired time. Intubation conditions were rated as excellent (easy passage of the endotracheal tube without coughing; vocal cords relaxed), good (passage of the tube with slight cough; vocal cords relaxed), poor (passage of the tube with moderate coughing or bucking; some vocal cord movement), or not possible (vocal cords adducted or not visualized; jaw not relaxed).

When the amplitude of T_1 recovered spontaneously to approximately 5% of baseline, an infusion of mivacurium (0.5 mg/mL) or succinylcholine (1 mg/mL) was started with an infusion pump and continued until neuromuscular blockade was no longer required. The initial infusion rates were 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for mivacurium and 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for succinylcholine and were adjusted in an attempt to maintain the level of block at 95 ± 4%. The steady-state infusion rate for individual patients was computed by averaging the infusion rates at 3-min intervals, beginning 6 min after the initiation of infusion and extending until the end of infusion. At the termination of infusion, approximately half of the mivacurium patients were allowed to recover spontaneously from neuromuscular block, and neuromuscular blockade in the other half was reversed with 0.045 mg/kg neostigmine and 0.02 mg/kg atropine. Stimulation was continued until T_1 reached at least 90% of baseline levels.

The times from administration of mivacurium or succinylcholine to 90% block, to maximum block, to start of recovery, and to 5% recovery of T_1 were recorded. The percent recovery at the termination of infusion and the times to 25%, 50%, 75%, 90%, and 95% recovery were also recorded, both in patients who recovered from neuromuscular blockade spontaneously and in patients given neostigmine. Systolic and diastolic blood pressures and heart rate were recorded before and at 2, 4, 6, 8, and 10 min after administration of the intubating dose of mivacurium or succinylcholine. Blood pressure was measured by oscillometry and heart rate was recorded from a Hewlett-Packard oscilloscope.

Neuromuscular, cardiovascular, and demographic data were analyzed and compared with use of the Duncan's multiple range test and Kruskal-Wallis one-way analysis of variance where appropriate. For some analyses (e.g., recovery times after termination of infusion), data from the two mivacurium dose groups were combined. Differences were considered statistically significant at $P < 0.05$. Unless otherwise specified, data are expressed as mean ± SD.

Table 1. Demographics in Groups of Patients Given Mivacurium (MIV) or Succinylcholine (SDC)

Group	*N*	Height (cm)	Weight (kg)	Age (yr)	Recovery Room Time (min)	Duration of Procedures (min)
SDC 1.0 mg/kg	10	154 ± 8	57 ± 9	27 ± 6	70 ± 23	61 ± 17
MIV 0.20 mg/kg	10	160 ± 8	63 ± 15	32 ± 12	74 ± 30	69 ± 22
MIV 0.25 mg/kg	10	152 ± 32	68 ± 19	28 ± 6	67 ± 12	68 ± 23
MIV 0.20 mg/kg + MIV 0.25 mg/kg	20	156 ± 23	65 ± 17	30 ± 10	70 ± 22	68 ± 22

Table 2. Time to Onset of Neuromuscular Blockade and Scores of Intubation Conditions in Patients Given Succinylcholine (SDC) or Mivacurium (MIV)

		Intubation Score at First Attempt† (Number of Patients)			
Group	TT90%*	Excellent	Good	Poor	Not Possible
SDC 1.0 mg/kg	0.9 ± 0.4	8/9 (89%)	1/10 (11%)	0	0
MIV 0.20 mg/kg	2.2 ± 0.8‡	7/10 (70%)	3/10 (30%)	0	0
MIV 0.25 mg/kg	1.5 ± 0.8‡	7/10 (70%)	3/10 (30%)	0	0

*Time to 90% suppression of T1.
†1 min after SDC; 2 min after MIV.
‡Significantly different from SDC group.

Results

There were no significant differences among the groups of patients given 0.2 mg/kg mivacurium, 0.25 mg/kg mivacurium, and 1.0 mg/kg succinylcholine with respect to height, weight, age, duration of surgery, or time in the recovery room (Table 1). There were also no demographic differences when data from two mivacurium dose groups were pooled and compared with data from the succinylcholine group.

The mean time from injection of muscle relaxant to 90% suppression of T_1 was significantly shorter in the succinylcholine group (0.9 min) than that in either mivacurium group (2.2 and 1.5 min) (Table 2). The mean time to 90% suppression of T_1 was approximately 45 sec shorter in patients given 0.25 mg/kg mivacurium than that in patients given 0.20 mg/kg mivacurium, but this difference was not statistically significant.

Owing to a technical difficulty that delayed the intubation attempt beyond the scheduled time, data for one succinylcholine patient were excluded from evaluation of intubation conditions. Table 2 shows that all other patients had their tracheas successfully intubated 1 min after 1.0 mg/kg succinylcholine or 2 min after 0.20 or 0.25 mg/kg mivacurium. Intubation conditions were rated as good or excellent in all patients. The proportions of patients accorded good or excellent scores were not different between the succinylcholine and mivacurium groups or between the two mivacurium groups.

Table 3. Duration fo Neuromuscular Blockade after Intubating Doses of Succinylcholine (SDC) or Mivacurium (MIV)

Group	*N*	Degree of Maximum Block (%)	Duration of Block* (min)
SDC 1.0 mg/kg	10	100	6.4 ± 1.4
MIV 0.20 mg/kg	10	100	12.7 ± 3.9†
MIV 0.25 mg/kg	10	99.7 ± 0.8	13.6 ± 3.8†

*Time from injection to reappearance of first visible twitch response.
†Significantly different from SDC group.

Twenty-nine of the 30 patients studied had complete (100%) suppression of T_1 after the initial intubating doses of succinylcholine or mivacurium (Table 3). One patient who received 0.25 mg/kg mivacurium developed 97% block. The duration of block, as evidenced by the time from administration of the intubating dose to the beginning of recovery of T_1, was significantly shorter in the succinylcholine group (6.4 min) than that in either of the mivacurium groups (12.7 and 13.6 min).

After initial recovery of T_1 after the intubating dose of relaxant, all patients received the same relaxants used for intubation, either succinylcholine or mivacurium, by continuous IV infusion to maintain block for the remainder of the procedure.

The duration of infusion ranged from 9 to 51 min in the succinylcholine patients and from 3 to 57 min in the patients given mivacurium (Table 4). On average, the initial infusion rates (60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for

Table 4. Infusion Requirements with Succinylcholine (SDC) and Mivacurium (MIV)

Group	N	Percent Block at Initiation of Infusion	Duration of Infusion (min)	Mean Infusion Rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
SDC	10	86.3 ± 10.4	26.1 ± 12.9 range 9–54	41.2 ± 14.2 range 22.5–60
MIV	20	95.7 ± 2.8	20.3 ± 13.8 range 3–57	6.6 ± 3.1* range 1.4–15

*N = 19.

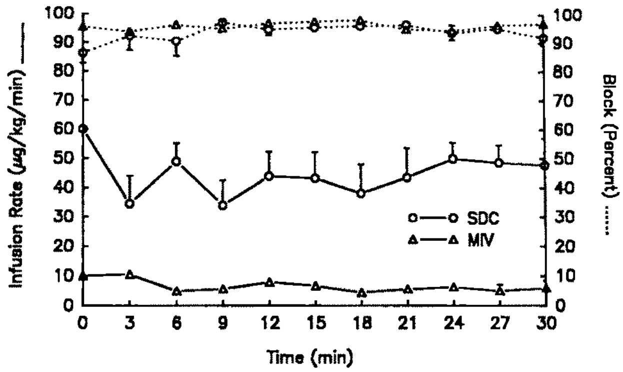


Figure 1. Mean infusion rates and degree (%) neuromuscular block in patients given succinylcholine or mivacurium. Mean ± SEM.

succinylcholine and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for mivacurium) were adjusted downward over the first few minutes after the start of infusion but became nearly constant thereafter (Figure 1). The mean infusion rates required to maintain approximately 95% block were 6.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for mivacurium and 41.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for succinylcholine (Table 4). Although the infusion rate for succinylcholine or mivacurium in a particular patient was relatively stable, once the initial adjustments had been made, the infusion requirements varied substantially among patients. Individual average infusion rates ranged from 1.4 to 15.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for mivacurium and from 22.5 to 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for succinylcholine.

Data on spontaneous recovery after cessation of infusion were available in ten succinylcholine and ten mivacurium patients (Table 5). Recovery of T_1 occurred more quickly with succinylcholine than it did with mivacurium. The mean time from termination of infusion to 95% recovery of T_1 was 6.5 min in patients given succinylcholine and 16.7 min for patients given mivacurium.

Nine patients given mivacurium had their neuromuscular blockade reversed with 0.045 mg/kg neostigmine. Of these, seven were reversed from a mean recovery of T_1 of 11.3% (range 1.3–21%). Among these 7 patients, recovery of T_1 to 95% of baseline levels occurred 7.6 ± 5.8 min after the dose of neostigmine. None of the patients given mivacurium required additional neostigmine.

There were no significant differences in systolic or diastolic pressures between the succinylcholine and mivacurium groups before relaxant administration or 2, 4, 8, or 10 min after administration (Figure 2). Six minutes after administration, no differences in blood pressure were evident between the succinylcholine group and the 0.20 mg/kg mivacurium group; however, systolic and diastolic pressures were significantly lower in patients given 0.25 mg/kg mivacurium than in those given 0.20 mg/kg mivacurium. There were no significant differences in heart rate before or after relaxant administration between the succinylcholine and mivacurium groups (Figure 3).

No adverse side effects were encountered in any patients. The time spent in the recovery room by patients given mivacurium was not significantly different from that in patients given succinylcholine and averaged approximately 70 min in each group.

Discussion

Because of its brief duration of action, succinylcholine is often employed when neuromuscular blockade is required in short inpatient or outpatient surgical procedure. The use of succinylcholine, however, is associated with a number of well-known disadvantages that may pose difficulties in patient management or threats to patient safety (11–14)—tachyphylaxis, phase II block, postoperative myalgia, bradydysrhythmias, hyperkalemia, and malignant hyperthermia. The use of the nondepolarizing agents, atracurium and vecuronium, has been advocated in short surgical procedures, but the intermediate duration of action of these relaxants may be too long in some instances. In two series of patients undergoing short (<30 min) intra-abdominal procedures in which atracurium or vecuronium were employed for intubation, Gyasi et al. (15,16) found no neuromuscular response or minimal response to train-of-four stimulation at the end of the procedure. Reversal of the neuromuscular blockade was attempted from a deep level of block in all patients, and 10% of the vecuronium patients and 15% of the atracurium patients required repeat doses of reversal agent to achieve clinically acceptable levels of recovery of neuromuscular function. Mivacurium, a nondepolarizing agent with relatively short duration of action and rapid recovery profile, may provide a useful alternative to succinylcholine, atracurium, or vecuronium in short cases.

Table 5. Spontaneous Recovery after Termination of Infusion of Succinylcholine (SDC) or Mivacurium (MIV)

Group	N	% Recovery at Termination of Infusion	Minutes between Termination of Infusion and Recovery to 25%‡	50%‡	75%‡	95%‡
SDC	10	4.3 ± 5.4	3.6 ± 1.7*	4.5 ± 2.0	5.7 ± 2.0	6.5 ± 2.8*
MIV	10	5.4 ± 4.9	8.2 ± 4.4†	11.5 ± 4.8†	14.2 ± 5.2†	16.7 ± 5.8†

*N = 9.
†Significantly different from SDC group.
‡Percent of baseline twitch response.

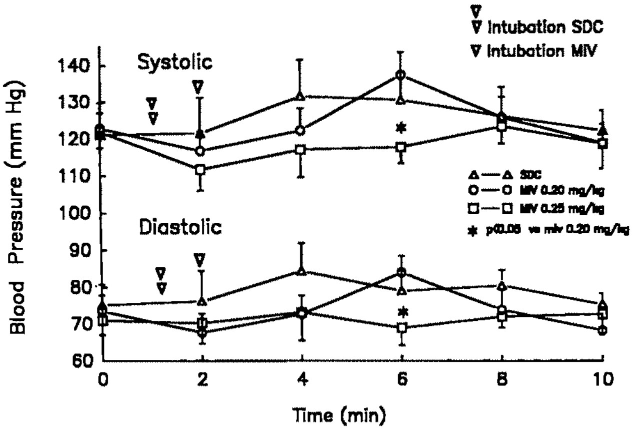


Figure 2. Systolic and diastolic blood pressures before and after succinylcholine (SDC) or mivacurium (MIV). Mean ± SEM. Muscle relaxant was administered at time 0. Intubation at 1 min in SDC group and 2 min in MIV groups.

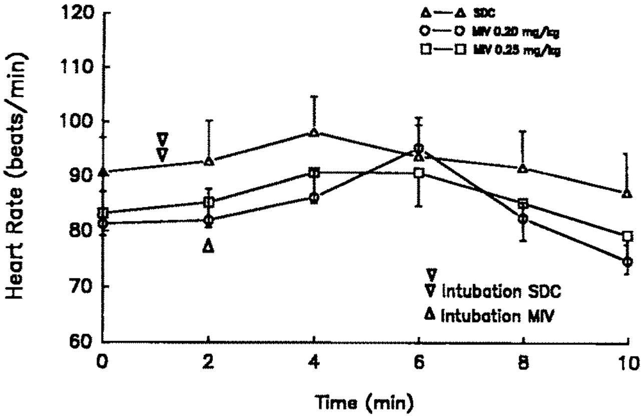


Figure 3. Heart rates before and after succinylcholine (SDC) or mivacurium (MIV). Mean ± SEM. Muscle relaxant was administered at time 0. Intubation at 1 min in SDC group and 2 min in MIV groups.

Our study of surgical outpatients managed with N_2O/O_2/narcotic anesthesia demonstrated that clinically acceptable intubation conditions were present 2 min after single bolus doses of 0.20 mg/kg (2.5 × ED_{95}) or 0.25 mg/kg (3 × ED_{95}). Savarese et al. (17) also reported good to excellent intubation conditions 2 min after single bolus doses of 0.25 mg/kg mivacurium administered to patients during thiopental-fentanyl induction. Clinically acceptable intubation conditions appear to be achievable within 1 to 1.5 min after doses of 0.25 mg/kg or 0.30 mg/kg administered in a priming sequence (17,18,19) but not sooner. Therefore, we elected to use 2 min as our time to intubation after mivacurium. In spite of the apparent effectiveness of priming on the onset of action of mivacurium, it is likely that succinylcholine will remain the neuromuscular blocking agent of choice for rapid-sequence intubation. In elective procedures, however, mivacurium may provide a useful nondepolarizing alternative to succinylcholine.

The duration of complete neuromuscular twitch suppression resulting from these intubating doses of mivacurium tested in our study was 13 min. This duration is about twice that of a conventional intubating dose of succinylcholine and, based on comparison with published literature (6–10), about ½ to ⅓ that of equipotent doses of atracurium or vecuronium. The duration of mivacurium action reported in the present study is consistent with that of data recently published by Savarese et al. (1) and others (2–5) under similar anesthetic conditions.

The short duration of action and rapid spontaneous recovery profile of mivacurium suggest that it would be useful as a continuous IV infusion to provide stable neuromuscular blockade. Infusion of neuromuscular blocking agents has obvious advantages over intermittent bolus dosing during long procedures but may be also applicable in short procedures in which only a few additional minutes of muscle relaxation are needed after the beginning of recovery from an initial intubating dose of relaxant. In the present study, neuromuscular block was readily maintained with mivacurium infusion. After an initial period of adjustment, small changes in infusion rate were required, reflecting the ease with which block could be controlled. The mean, stable-state infusion rate for mivacurium in our study population was 6.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which is consistent with values of 4.4–8.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in abstract form reported by others (2,20,21) for adult patients managed with N_2O/O_2/narcotic anesthesia.

In an individual patient, the rate of mivacurium infusion necessary to maintain a stable level of blockade was relatively constant over time. However, considerable variation in average infusion rates (1.4–15.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was noted among individual patients. A similar degree of variation has been reported for patients who received atracurium (22–25) or vecuronium (26–28) by infusion and underscores the need for individualization of dosing and adequate monitoring of neuromuscular block.

Although spontaneous recovery from mivacurium-induced neuromuscular block was significantly slower than that after succinylcholine, historical comparisons indicate that spontaneous recovery after mivacurium appears to be considerably faster than that after other nondepolarizing agents. The time from beginning of recovery to 95% recovery (17 min) and the 25–75% recovery index (6 min) observed for mivacurium in this study are approximately ½ of the values reported for the intermediate-acting agents atracurium and vecuronium (29).

Reversal of mivacurium-induced block with a single dose of 0.045 mg/kg neostigmine was rapid, even from relatively deep levels of block. Patients in whom neostigmine was given when there was approximately 11% recovery of T_1 reached 95% recovery of T_1 in a mean time of 7.6 min. None of the mivacurium patients required supplemental doses of neostigmine to achieve clinically adequate recovery of neuromuscular function.

A transient decrease in blood pressure in some patients, presumably due to endogenous release of histamine, has been reported by others (30–31) after the doses of mivacurium employed in this study. No clinically significant cardiovascular differences were noted among patients intubated with succinylcholine or with mivacurium in the present study. However, the experimental design employed (i.e., placement of the endotracheal tube shortly after administration of the intubating dose of muscle relaxant) and times at which blood pressure was measured did not permit detailed comparisons of the cardiovascular effects associated with intubating doses of succinylcholine or mivacurium. Under the conditions of our study, it is likely that any cardiovascular effects of mivacurium would have been masked by the cardiovascular changes associated with intubation (32). It is possible that the difference in blood pressure noted between the 0.25 mg/kg mivacurium group and the 0.20 mg/kg mivacurium group at 6 min in Figure 2 might be related to histamine-induced hypotension that was only partly offset by the effects of intubation. The absence of cutaneous flushing and the relatively long period of time between administration of the dose and the peak blood pressure effects in the 0.25 mg/kg mivacurium group, however, argue against this explanation.

In their study of outpatients, McPeek et al. (19) noted that time spent in the recovery room was approximately 40 min longer for patients given succinylcholine than for patients given mivacurium. No differences in times spent in the recovery room between patients given mivacurium and succinylcholine were noted in our study. The basis for the discrepancy between our results and those of McPeek et al. (19) remain unclear. Furthermore, our study is the first to compare the two medications in a blind fashion when utilized at intubating doses in patients having brief surgery.

In conclusion, the results of the present study suggest that mivacurium may be a useful adjunct to general anesthesia when a nondepolarizing alternative to succinylcholine is desired for the management of short, elective outpatient procedures.

We thank Alexander Marr, CRNA, and Jennifer Lessin, RN, without whose expert assistance this study would not have been possible.

References

1. Savarese JJ, Ali HH, Basta SJ, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 1988;68:723–32.
2. Brandom BW, Weber S, Cook DR, et al. Comparison of the effects of BW 1090U and succinylcholine administered by bolus and infusion in anesthetized patients. Anesthesiology 1986; 65:A288.
3. Choi WW, Mehta MP, Murray DJ, et al. Neuromuscular effects of BW B1090U during narcotic nitrous oxide anesthesia. Anesthesiology 1987;67:A355.
4. Lee C, Cheng M, Yang E, et al. Dose-duration relationship of BW 1090U by bolus injections. Anesthesiology 1987;67:A353.
5. Lee C, Cheng M, Yang E, et al. Neuromuscular effects of BW 1090U in patients under narcotic-N2O anesthesia. Anesthesiology 1987;67:A354.
6. Scott RPF, Savarese JJ, Basta SJ, et al. Clinical pharmacology of atracurium given in high dose. Br J Anaesth 1986;58:834–8.
7. Ali HH, Basta SJ, Savarese JJ, et al. Single twitch and train-of-four responses for atracurium and vecuronium. Anesth Analg 1985;64:187.
8. Gramstad L, Lilleaasen P. Dose-response relation for atracurium, ORG NC45, and pancuronium. Br J Anaesth 1982; 54:647–51.
9. Agoston S, Salt P, Newton B, Bencini A, Boomsma P, Erdmann W. The neuromuscular blocking action of ORG NC45, a new pancuronium derivative, in anaesthetized patients. Br J Anaesth 1980;52:53S–9S.

10. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P. Clinical pharmacology of ORG NC45 (Norcuron TM). A new non-depolarizing muscle relaxant. Anesthesiology 1981;55:6–11.
11. Cook DR. Muscle relaxants in infants and children. Anesth Analg 1988;160:335–43.
12. Durant NN, Katz RL. Suxamethonium. Br J Anaesth 1982; 54:195–208.
13. Goudsouzian N, Gionfriddo M. Muscle relaxants and children. Sem Anesthesiol 1984;3:50–8.
14. Lee C. Succinylcholine: its past, present and future. In: Katz RL ed. Muscle relaxants: basic and clinical aspects. Orlando: Grune & Stratton, 1984:69–85.
15. Gyasi HK, Naguib M, Adu-Gayamfi Y. Atracurium for short surgical procedures: a comparison with succinylcholine. Can Anaesth Soc J 1985;32:613–7.
16. Gyasi HK, Williams A, Melloni C, Bevan DR: ORG NC45 for short intra-abdominal operations: A comparison with succinylcholine. Can Anaesth Soc J 1983;30:132–5.
17. Savarese JJ, Ali HH, Basta SJ, et al. Ninety and 20-second tracheal intubation with BW B1090U: clinical conditions with and without priming after fentanyl-thiopental induction. Anesthesiology 1987;65:A283.
18. Savarese JJ, Ali HH, Basta SJ, Embre PB, Risner ME. Sixty-second tracheal intubation with BW B1090U after fentanyl-thiopental induction. Anesthesiology 1987;67:A351.
19. McPeek JB, Nozik DH, Walzer SG, Embree PB, Schwartz A. Comparison of BW B1090U with succinylcholine to facilitate endotracheal intubation in an outpatient surgical unit. Anesthesiology 1987;67:A352.
20. Ali HH, Savarese JJ, Embree PB, et al. Clinical pharmacology of BW B1090U continuous infusion. Anesthesiology 1986;65: A282.
21. Powers D, Weber S, Brandom BW, et al. BW B1090U infusion requirements in adults during isoflurane or narcotic anesthesia. Anesthesiology 1987;67:A359.
22. Cheng M, Lee C, Yang E, Cantley E. Mivacurium chloride infusion during nitrous-narcotic anesthesia. Washington, D.C.: Proc 9th World Congr Anaesth, May 22–28, 1988:A0532.
23. D'Hollander AA, Luyckz E, Barvais L, DeVille A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. Anesthesiology 1983;59:237–40.
24. Eager BM, Flynn PJ, Hughes R. Infusion of atracurium for long surgical procedures. Br J Anaesth 1984;56:447–51.
25. Gargarian MA, Basta SJ, Savarese JJ, et al. The efficacy of atracurium by continuous infusion. Anesthesiology 1984; 61:A291.
26. D'Hollander AA, Czerucki R, DeVille A, Cuvelier F. Stable muscle relaxation during abdominal surgery using combined intravenous bolus and demand infusion: clinical appraisal with ORG NC45. Can Anaesth Soc J 1982;29:136–41.
27. D'Hollander A, Massaux F, Nevelsteen M, Agoston S. Age-dependent dose-response relationship of ORG NC45 in anesthetized patients. Br J Anaesth 1982;54:653–7.
28. Mirakhur RK, Ferres CJ, Pandit SK. Muscle relaxation with an infusion of vecuronium. Anesthesiology 1984;61:A293.
29. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. Anesthesiology 1984;61:444–53.
30. Savarese JJ, Basta SJ, Ali HH, et al. Cardiovascular effects of BW 1090U in patients under nitrous oxide-oxygen-thiopental-fentanyl anesthesia. Anesthesiology 1985;63:A319.
31. Forbes RB, Choi WW, Mehta MP, et al. Cardiovascular effects of BW B1090U during nitrous oxide-oxygen-narcotic anesthesia. Anesthesiology 1987;67:A360.
32. Stoelting RK. Endotracheal intubation. In: Miller RD, ed. Anesthesia, 2nd ed. New York: Churchill Livingstone, 1986: 233–55.

ANESTH ANALG
1989;69:100–12

Review Article

Calcium, Calmodulin, and Anesthesiology

Dennis F. Landers, MD, PhD, Gerald L. Becker, MD, and K. C. Wong, MD, PhD*

Key Words: IONS—calcium.

In the course of their work, anesthesiologists exercise substantial control over vital physiological functions in their patients. Levels of consciousness and pain, myocardial contractility, vascular resistance, alveolar ventilation and skeletal muscle relaxation are principal concerns of the clinician, who monitors them closely and manipulates them as necessary by pharmacological or other means. Each of these critical processes has long been known to be strongly regulated by intracellular calcium levels in neural or muscular tissue (1–3). This article will review such mechanisms of calcium-mediated regulation, emphasizing examples important to anesthesiologists. Particular attention will be given to ways in which calcium and its principal intracellular receptor/mediator calmodulin (4,5) are known (or surmised) to interact with anesthetics, other drugs, and other aspects of anesthetic management in the overall control of tissue function.

Before considering further the interplay between anesthetic interventions and calcium in tissue regulation, we must review calcium's role as a regulator under normal physiological conditions. Despite the diversity of the tissue/processes just listed, there are underlying similarities in the way calcium functions (3,4). In all cases, regulation begins with a specific extracellular stimulus—electrical or chemical—and ends with a specific intracellular response. However, the stimulus terminates at the plasma membrane and does not react directly with the intracellular component(s) producing the response. Instead, the stimulus causes an increase in cytoplasmic ionized calcium concentration, which in turn triggers the response. In other words, calcium serves as a so-called "second messenger" (3), analogous to cyclic adenosine monophosphate (cyclic AMP). A second messenger acts intracellularly to link a specific extracellular stimulus (considered the first messenger) to a response specific for that cell type. The cyclic AMP system, along with the general concept of second messengers in stimulus-response coupling, was elegantly reviewed for anesthesiologists by Maze (6) in 1981. Cyclic AMP has been found to mediate the intracellular effects of a variety of external chemical signals, mainly hormonal. Comparable evidence now supports the hypothesis that calcium rather than cyclic AMP fills the second messenger role in various other instances of stimulus-response coupling. Calcium is recognized as the preeminent mediator of rapid responses to electrical stimulation, typified by neurotransmission and cardiac and skeletal muscle contraction (3). However, the list of important calcium-dependent processes also includes smooth muscle contraction, DNA replication and chromosomal movement in mitosis, motility in nonmuscle cells, hepatic glycogen mobilization, and certain substrate oxidations supporting mitochondrial energy generation (3–5).

Whereas the intracellular regulatory effects of cyclic AMP are expressed by its binding to and activation of a specific protein kinase, the receptor and mediator entities for calcium messages are more diverse and are still being elucidated (3,4). In recent years, a number of proteins have been identified having properties compatible with their serving as intracellular receptors for calcium and mediators of its regulatory effects (Figure 1): they show concentration-dependent binding of free calcium over its cytoplasmic concentration range (0.1–1.0 μM), and they are found in proximity to calcium-activated enzyme systems (5). However, a single protein species, cal-

---

Received from the Department of Anesthesiology, University of Nebraska Medical Center, Omaha, Nebraska and the *Department of Anesthesiology, University of Utah, Salt Lake City, Utah. Accepted for publication February 9, 1989.

Address correspondence to Dr. Landers, Department of Anesthesiology, University of Nebraska Medical Center, 42nd and Dewey Avenue, Omaha, NE 68105.

©1989 by the International Anesthesia Research Society

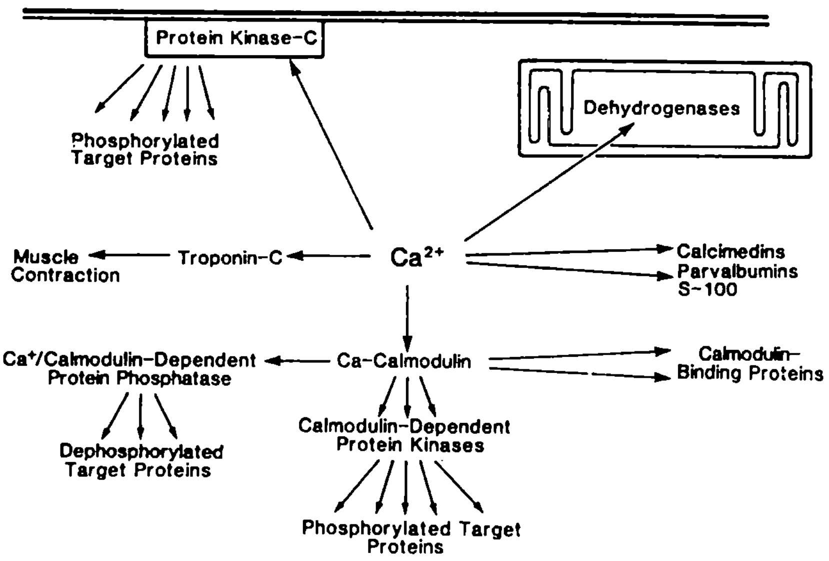

Protein Kinase-C
Phosphorylated Target Proteins
Dehydrogenases
Muscle Contraction
Troponin-C
Ca^{2+}
Calcimedins
Parvalbumins
S-100
Ca+/Calmodulin-Dependent Protein Phosphatase
Ca-Calmodulin
Calmodulin-Binding Proteins
Dephosphorylated Target Proteins
Calmodulin-Dependent Protein Kinases
Phosphorylated Target Proteins

Figure 1. The interaction of calcium with intracellular proteins. The concentration of Ca^{2+} in the cytoplasm can increase either through an influx from the extracellular space through the plasma membrane or by release from intracellular stores. Not all of the proteins shown are present in all cell types, and in particular, the target proteins phosphorylated by the protein kinases are often tissue specific. (Reprinted with permission from England PJ. Br Med Bull 1986; 42:375–83).

modulin, dominates the field of calcium receptor-mediators, much as cyclic AMP-dependent protein kinase is the common mediator of cyclic AMP messages in a wide variety of cell types (7–12). Many eucaryotic cells also contain additional calcium-binding proteins (summarized in Table 1) (13), but these proteins are for the most part quite specialized for a particular tissue and function and are, therefore, of less general interest than is calmodulin (14–16). Calmodulin activates many different enzymes (Table 2) in so many cell types that virtually every biomedical discipline concerns itself to some extent with the consequences of calmodulin's action(s). Of particular relevance to anesthesiology are the following, each of which will be discussed in more detail later in this article: Calcium binding to calmodulin (or a homologous protein) is a crucial step in activating neurotransmitter release in all types of nerve cells and contraction of skeletal, cardiac, and smooth muscle. Calmodulin, because it affects enzymes and other proteins that are themselves regulators of second messenger systems, stands to control neural and muscular function on two different levels because processes in these tissues are modulated by cyclic AMP as well as by calcium. Derangement of intracellular calcium homeostasis, and perhaps also the operation of calcium receptor-mediator(s), has been implicated in the pathogenesis of malignant hyperthermia. Finally, drugs used by anesthesiologists may act directly on calmodulin to alter its calcium- or enzyme-binding properties and thereby its regulatory ability.

Table 1. Intracellular Ca^{2+}-Binding Proteins

Protein	MW	Ca^{2+} Binding Sites	Proposed Function
Calmodulin	16,700	4	Multifunctional
α-Parvalbumin	11,500	2	Ca^{2+} sink
β-Parvalbumin	11,500	2	Ca^{2+} sink
Regulatory myosin light chain		1	Regulation of contraction
Essential myosin light chain		0	
Skeletal muscle troponin C	17,900	4	Regulation of contraction
Cardiac muscle troponin C		3	Regulation of contraction
Intestinal Ca^{2+}-binding protein	8,500	2	Unknown
Calcineurin B	19,200	4	Protein dephosphorylation
S 100 α	10,400	1	Regulation of cytoskeleton
S 100 β	10,507	1	Regulation of cytoskeleton
Oncomodulin	11,500	2	Unknown
Rat skin Ca^{2+}-binding protein	12,000	2	Unknown
Tetrahymena Ca^{2+}-binding protein (TCBP 10)	10,000	1	Unknown
Brain Ca^{2+}-binding protein (caligulin)	24,000	1	Unknown
Brain Ca^{2+}-binding protein (CBP-18)	18,000	1	Unknown

(Reprinted with permission from Manalan AS, Klee CB. Calmodulin. Adv Cyclic Nucleotide Protein Phosphorylation Res 1984;18:227–8.)

Distribution of Calmodulin

Calmodulin has a widespread distribution (17) and has been purified from many sources including porcine brain (18), bovine brain (19), bovine heart (10), bovine adrenal medulla (20), and rat testis (21). The richest source of calmodulin is the specialized electric

Table 2. Calmodulin-Regulated Enzymes

Enzyme
Cyclic nucleotide phosphodiesterase
Adenylate cyclase
Guanylate cyclase
Ca^{2+}-ATPase
Myosin light chain kinase
Phosphorylase kinase
Glycogen synthetase kinase
Ca^{2+}-dependent protein kinase
NAD kinase

The table lists enzymes with activities that are clearly dependent on calmodulin. Although Ca^{2+}-dependent protein kinase(s) has been reported in numerous tissues, the enzyme has not been characterized vigorously. (Reprinted with permission from Cheung WY. Prog Brain Res 1982; 56:237–53.

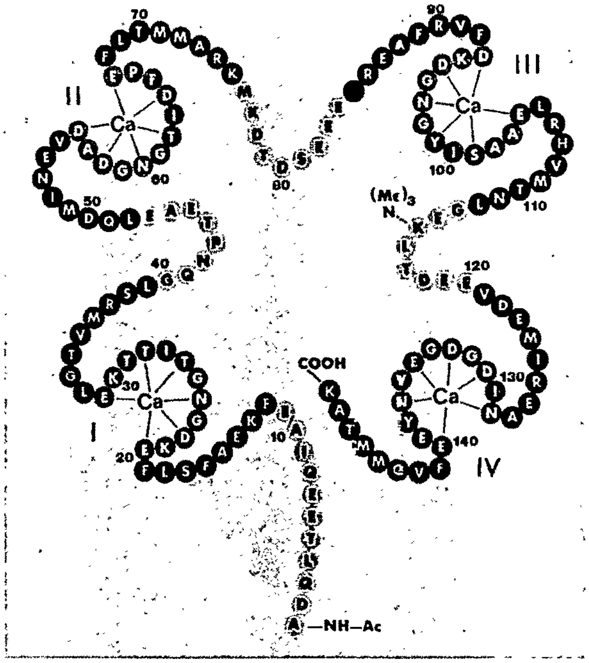


Figure 2. Amino acid sequence of bovine brain calmodulin. The sequence was elucidated by Watterson et al. (31). The scheme depicts the four putative Ca^{2+}-binding domains, each consisting of a 12-residue loop (**gray circles**) flanked on each side by an 8-residue helix (**dark circles**) as proposed by Kretsinger (5). The predicted Ca^{2+}-binding residues are indicated by the **solid lines** in each loop. The amino acids are abbreviated: A = alanine; D = aspartic acid; E = glutamic acid; F = phenylalanine; G = glycine; H = histidine; I = isoleucine; K = lysine; L = leucine; M = methionine; N = asparagine; P = proline; Q = glutamine; R = arginine; S = serine; T = threonine; V = valine; Y = tyrosine. (Reprinted with permission from Cheung WY. Harvey Lect 1985;79:173–216.)

organ of the electric eel, *Electrophorus electricus,* where it composes more than 2% of the total protein (22). Calmodulin is apparently ubiquitous in mammalian tissues, having been reported in erythrocytes, platelets, adipocytes, liver, kidney, testis, brain, adrenal, thymus, and bone marrow (17). Among mammalian tissues, brain and testis have the highest concentrations of calmodulin. In brain, calmodulin levels are highest in the caudate-putamen and frontal cortex and lowest in pons and medulla, thus being richer in grey matter and poorer in white matter (23). The subcellular localization of calmodulin has been studied in many different tissue types. Calmodulin is found free in the cytoplasm as well as in association with membrane and organelles; the proportion of free to bound apparently varies with cell type. Studies using homogenates of rat cerebral cortex show that the distribution of calmodulin between a 100,000 g × 60 min supernate and pellet is dependent upon the concentration of free calcium in the homogenizing medium (24). In medium with excess chelating agent added to deplete free calcium, 77% of the calmodulin was soluble and 22% particulate-associated, whereas in medium containing 100 μM calcium, only 58% of calmodulin was soluble and 42% was particulate-associated. These findings suggest that calmodulin undergoes a calcium-dependent association with a factor or factors present in the particulate preparation, and that the subcellular distribution of calmodulin will be affected by conditions that prevail during in vitro tissue preparation (25). It appears that the binding of calmodulin to particular fractions requires calcium and occurs at specific sites (26). This binding is saturable, reversible, and temperature- and trypsin-sensitive. Recently, calmodulin was found by use of an indirect immunohistochemical fluorescent localization technique (27) to be generally distributed throughout the cytoplasm of interphase proliferating cultured cells (27). During mitosis, much of the calmodulin appeared to associate with the mitotic apparatus. Another study using tissue slices of rat liver demonstrated that calmodulin is associated with cytoplasm, nucleus, plasma membrane, and glycogen particles (28). Similar distributions were found in slices of skeletal muscle and adrenal gland.

Physicochemical Properties of Calmodulin

Primary Structure

Calmodulin molecules from many different tissues and species show a striking degree of homology (13,29). All consist of a single polypeptide chain of 148 amino acids representing a molecular weight of 16,723 daltons (30). One-third of the residues are aspartate and glutamate, which furnish carboxyl groups to chelate calcium. The primary structure of calmodulin, as shown in Figure 2, includes four calcium binding domains (31–33). The dissociation constant of these sites for calcium is about 10^{-6} M, within the physiologic concentration range for the free cation. This property allows calmodulin to respond to changes in calcium levels over the typical intracellular concentration range, which is an essential property for calmodulin's being a calcium receptor. Calmodulin in the presence of calcium resists denaturation when exposed to conditions such as boiling, eight molar concentration (8 M) urea, and acidic pH that would denature most other proteins (30–32).

Calcium-Induced Conformational Change

The amino acid composition of calmodulin is notable for the absence of cysteine and tryptophan. Proline, which usually appears at bends of a polypeptide and prevents formation of helical structure, is also absent (30). Because there is no cysteine present within the calmodulin molecule, there can be no formation of disulfide bridges; therefore, the calmodulin molecule is highly flexible and easily resumes its original form after it has been distorted. This inherent flexibility allows calmodulin to effectively communicate the calcium signal by undergoing a substantial conformational change, which is crucial in enabling target proteins to bind to calmodulin (30,32).

There have been many studies of the divalent cation binding properties of calmodulin; one of the most detailed studies is that of Wolff et al. (34). They found that when binding was measured with calcium as the sole source of divalent cation, a total of four molecules of calcium bound per molecule of calmodulin: 3 Ca^{2+} at sites with a dissociation constant of 0.2 μM and 1 Ca^{2+} at a site with a dissociation constant of 1 μM. These and other studies established the existence of two classes of binding sites on calmodulin. Many different probes have shown substantial conformational changes of calmodulin after binding of calcium that are consistent with an increase in helical content and a decrease in random coil. Therefore, the calmodulin assumes a more compact structure with calcium (18,34–36). This shift to a more compact structure is likely to be involved in enzymatic activation, perhaps by increasing the availability of a hydrophobic region capable of interacting with the inactive enzyme to alter its own conformation, thereby activating it (19,37,38).

Many experiments using a calmodulin-phosphodiesterase system have shown that calcium initially changes the calmodulin to form a calcium-calmodulin complex that is capable of activating the enzyme (8,10,19,36,39). This complex then associates with the enzyme forming an activated complex, which presumably involves a change in enzyme conformation as outlined here.

$$n\ \mathrm{Ca}^{++} + (\mathrm{calmodulin})_{\mathrm{inactive}} \rightarrow (\mathrm{Ca}^{++}{}_{n}\cdot\mathrm{calmodulin}^{*})_{\mathrm{active}}$$

$$(\mathrm{Ca}^{++}{}_{n}\cdot\mathrm{calmodulin}^{*})_{\mathrm{active}} + (\mathrm{E})_{\mathrm{inactive}} \rightarrow (\mathrm{Ca}^{++}{}_{n}\cdot\mathrm{calmodulin}^{*}\cdot\mathrm{E}^{*})_{\mathrm{active}}.$$

The asterisk indicates a new configuration, and "*n*" indicates the number of bound calcium ions. Kinetic analysis has shown that calmodulin assumes its active conformation with three or four bound calcium ions. Several interesting speculations can be made from this model. It is clear that an increase of calcium elicits a change in the calmodulin that serves as a signal transmitted to the enzyme to change its activity. These reactions are reversible, and the direction of the reaction is determined by the intracellular level of free calcium, which is known to increase from near 10^{-7} M to near 10^{-6} M when cells are stimulated. It has also been suggested that minor increases in intracellular free calcium could activate enzymes with a high affinity for the calcium-calmodulin complex without activating enzymes with lower affinity (33).

Role of Calmodulin in the Calcium Messenger System

Calcium as a Messenger

Among the divalent cations, only calcium has been shown to serve as a messenger (4,40,41). Although calcium is ubiquitous and abundant in all biologic systems, the hallmark of its cellular metabolism and the basis for its ability to act as a messenger is the tight regulation of the ionized (free) fraction of cytoplasmic total calcium at relatively low levels (10^{-7} M) under resting conditions. The free calcium concentration in the extracellular fluid is therefore some 1,000 to 10,000 times higher than the baseline calcium level in the cytosol. This gradient is maintained by a low natural permeability of the plasma membrane to calcium and by at least 2 adenosine triphosphate (ATP)-dependent mechanisms in the plasma membrane by which calcium is continuously pumped out of the cell. When the cell is stimulated, transient increases in the cytoplasmic calcium concentration occur as a result of a rapid increase in the rate of plasma membrane calcium influx via one of several types of specific calcium channels or an increase in the release of calcium from an intracellular organelle or both (3). The period of increased calcium within the cell is generally brief, because the cation is immediately subject to removal from the cytoplasm by the calcium pumps located in the plasma membrane and in the membranes of mitochondria and endoplasmic (sarcoplasmic) reticulum (42).

Some divalent cations such as barium or strontium have an ionic radius appreciably larger than Ca^{++} and are virtually inactive in their ability to stimulate calmodulin-dependent phosphodiesterase. Magnesium (Mg^{2+}) has a considerably smaller ionic radius than does Ca^{2+}; thus despite its many-fold higher concentration than Ca^{2+} throughout the cell, Mg^{2+} also competes ineffectively for Ca^{2+} binding sites on the calmodulin molecule. Divalent cations such as lead (Pb^{++}), cadmium (Cd^{++}), or mercury (Hg^{++}) are much closer in size to Ca^{2+} and readily substitute for calcium (Ca^{++}) in binding to calmodulin. These latter ions are not normally present at concentrations comparable to Ca^{2+} in living systems; however, when present at elevated levels as environmental pollutants, these ions can cause significant metal toxicity after making their way into cells (30,40,41).

Outline of the Calcium Messenger System

In contrast to the cyclic AMP system, the "functional anatomy" of the calcium messenger system differs among the various tissues in which that system operates (3,4). The largest differences are between the excitable and non-excitable tissues. A major difference is in the nature of the activating stimulus: first messages are electrical in nerve and in cardiac and skeletal muscle, whereas nonexcitable tissues are activated by chemical stimuli (3,43). In nerve and cardiac muscle, depolarization promotes entry of calcium into the cytoplasm via voltage-dependent calcium channels in the plasma membrane. In nerve, this process generates enough calcium to serve as the second messenger for neurotransmitter release. In cardiac muscle, the voltage-dependent calcium influx is transmitted via the transverse tubules, triggering the release of additional, true second messenger calcium from sarcoplasmic reticulum (Ca^{++}-induced Ca^{++} release). In skeletal muscle, depolarization of the plasma membrane is either transmitted through the T-system directly to the sarcoplasmic reticulum, which then releases the calcium that activates contraction, or, as in cardiac muscle, there is trigger calcium-induced release of Ca^{++} from sarcoplasmic reticulum. In skeletal muscle, the voltage-activated Ca^{++} channel appears to be preferentially localized near the t-tubular region of the sarcolemma, whereas Ca^{++} channels in cardiac muscle appear to be distributed throughout the sarcolemmal membrane.

In non-excitable tissues, as with skeletal muscle, second messenger calcium appears to be derived from internal stores (43). However, in non-excitable tissues, intracellular calcium release is triggered by a *chemical* signal generated by an effector, phospholipase C, at the cytoplasmic surface of the plasma membrane (44). That enzyme cleaves a minor membrane phospholipid, phosphatidylinositol biphosphate, to form inositol triphosphate plus diacylglycerol. This step is important because it gives rise to a calcium messenger system with two separate "pathways" that can complement each other in mediating calcium-dependent intracellular events (45).

Because inositol trisphosphate is highly water-soluble, it rapidly diffuses through the cytoplasm to the endoplasmic reticulum, where it triggers release of stored calcium. The resulting rapid and generally transient increase in cytoplasmic calcium initiates formation of a calcium-calmodulin complex, which appears to mediate mainly short-term calcium-regulated effects, such as neurotransmitter release. Most of the enzymes activated by the calcium-calmodulin complex are protein kinases, which act on one or more specific proteins as substrate(s), phosphorylating specific amino acid side chains (4,13). The calcium and cyclic AMP messenger systems are similar in that both mediate intracellular responses chiefly via activation of protein kinases. However, as at other levels of organization, the calcium system shows greater complexity: different—and in some cases multiple—kinase species are activated in different cell types. A frequent situation is for kinases of both broad and narrow specificity to be activated in the same cell type by the same calcium message. In liver, for example, the calcium-calmodulin complex activates both a protein kinase of broad substrate specificity and also phosphorylase kinase (46). The latter phosphorylates only a single substrate, glycogen phosphorylase, which in turn catalyzes the rate-limiting step in the breakdown of glycogen to glucose. Another complexity of the calcium messenger system is that in some cases the intensity of calcium-dependent response does not parallel the extent of cytoplasmic calcium increase (3). This occurrence is especially likely with a sustained response—i.e., one lasting more than a few seconds after a single activating stimulus. In such situations, the magnitude of the calcium message peaks, then declines as the cytoplasmic free calcium level returns toward its baseline value for that cell type. The continued manifestation of a calcium-dependent response in the face of a declining value of cytoplasmic calcium is mediated by the second "pathway" of the calcium messenger system, involving a receptor/activator entity known as protein kinase C (47). The diacylglycerol produced by phospholipase C, in combination with the second messenger calcium released by inositol trisphosphate, activates protein kinase C by increasing its

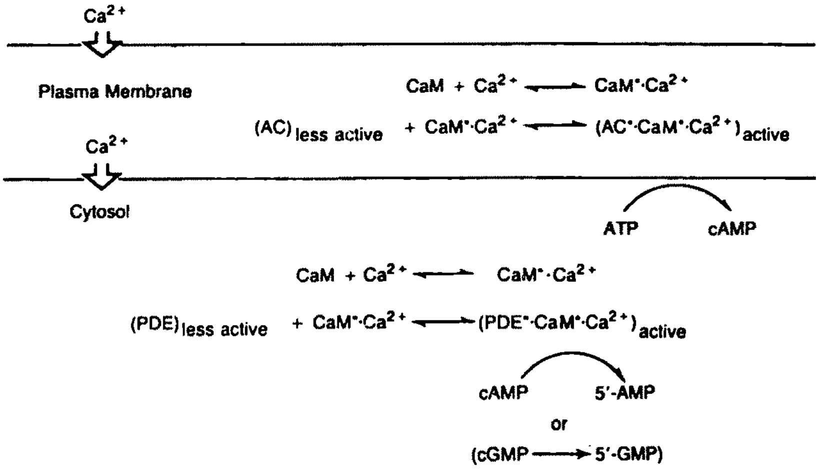

Ca^{2+}
Plasma Membrane
Ca^{2+}
Cytosol
$CaM + Ca^{2+} \rightleftharpoons CaM^{*}{\cdot}Ca^{2+}$
$(AC)_{less\ active} + CaM^{*}{\cdot}Ca^{2+} \rightleftharpoons (AC^{*}{\cdot}CaM^{*}{\cdot}Ca^{2+})_{active}$
ATP
cAMP
$CaM + Ca^{2+} \rightleftharpoons CaM^{*}{\cdot}Ca^{2+}$
$(PDE)_{less\ active} + CaM^{*}{\cdot}Ca^{2+} \rightleftharpoons (PDE^{*}{\cdot}CaM^{*}{\cdot}Ca^{2+})_{active}$
cAMP
5'-AMP
or
(cGMP → 5'-GMP)

Figure 3. Speculative scheme for the sequential activation of brain adenylate cyclase and phosphodiesterase by a cellular flux of Ca^{2+}. *Indicates an active conformation. AC = adenylate cyclase; CaM = calmodulin; PDE = phosphodiesterase. (Reprinted with permission from Cheung WY. Harvey Lect 1985;79:173–216.)

sensitivity to calcium, so that it remains active even after cytoplasmic calcium has returned to baseline levels (48).

Biologic Functions of Calmodulin

Regulation of Cyclic AMP Messenger System via Activation of Adenylate Cyclase and Phosphodiesterase

Cyclic nucleotide metabolism in intact brain tissue is activated by many external stimuli such as peptides, adenosine, biogenic amines, and physical or nonspecific factors that induce depolarization (49). Extracellular calcium or adenosine was found to be an absolute requirement for norepinephrine or histamine–stimulated cyclic AMP formation in brain slices (50). Other studies have demonstrated that intracellular cyclic AMP formation occurs in response to catecholamines and is coupled to calcium metabolism. After noting the similarity in the calcium requirement between adenylate cyclase and phosphodiesterase, first Brostrom et al. (14) and then Cheung et al. (51) showed that calmodulin regulated adenylate cyclase. The activation of adenylate cyclase and phosphodiesterase by calmodulin probably does not occur simultaneously because concurrent activation would be wasteful. As illustrated in Figure 3, adenylate cyclase is associated with the cell membrane, whereas calcium dependent phosphodiesterase is located within the cytoplasm (52). Stimulation of a cell by humoral factors such as biogenic amines, or factors inducing depolarization such as electrical impulse lead to an influx of calcium ions. As calcium enters the submembrane region, it activates the synthesizing enzyme (adenylate cyclase); with subsequent further diffusion into the cytoplasm, calcium activates the hydrolytic enzyme (phosphodiesterase). Alternatively, the calcium sensitivities of the two enzymes may differ, thereby allowing the sequential activation of adenylate cyclase and phosphodiesterase (53). During the initial phase of calcium influx, low levels of calcium activate adenylate cyclase. As calcium continues to increase, it then inhibits adenylate cyclase while it activates phosphodiesterase, thus returning intracellular cyclic AMP to its steady state level.

Regulation of Calcium Messenger System via Activation of Plasma Membrane Calcium Pump

The calcium active transport system most widely present in the plasma membranes of eucaryotic cell types is an ATPase commonly referred to as "the calcium pump" (54). It typically has a relatively high affinity for calcium binding but catalyzes a relatively low rate of calcium transport. Its principal role is therefore to "fine-tune" the rate of calcium elimination from the cytoplasm so as to regulate the free calcium level within the narrow limits prescribed for that compartment (55). In all cell types, with the notable exception of liver, the activity of this calcium pump is enhanced by the direct binding of calcium-calmodulin complex to one or both of the enzyme's two catalytic subunits (56,57). This regulatory arrangement endows calmodulin with feedback control over the calcium increases that promote calmodulin-mediated cellular responses.

Calmodulin and Troponin C in Muscle Contraction and Metabolism

Physiologists have known since 1947 that there was a contractile response following the injection of calcium

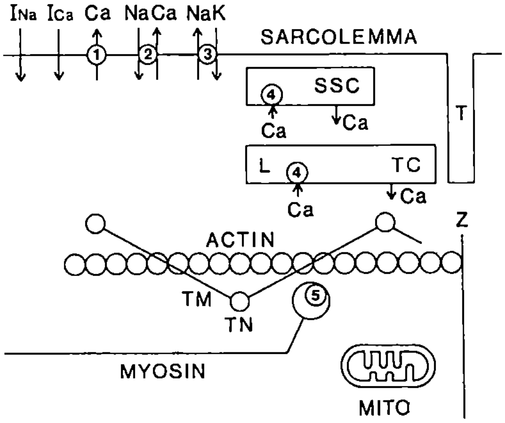


Figure 4. Schematic diagram of actin and myosin filaments, regulatory proteins, and the organelles that control myocardial ion fluxes. Z = Z line of sarcomere; TN = troponin; TM = Tropomyosin; T = transverse tubule; TC = terminal cisternal portion of sarcoplasmic reticulum (SR); L = longitudinal portion of SR; SSC = subsarcolemmal cisternal portion of SR; 1 = sarcolemmal Ca^{2+}-ATPase; 2 = sarcolemmal Na^+/Ca^{2+} exchange mechanism; 3 = sarcolemmal Na^+/K^+ pump; 4 = SR Ca^{2+}-ATPase; 5 = myosin ATPase; I_{Na} and I_{Ca} = inward sodium and calcium currents. (Reprinted with permission from Rusy BF. Anesthesiology. 1987; 67:745–66.

into a muscle fiber (2). We now know that electromechanical coupling, a series of events that begins with depolarization of the muscle cell membrane and ends with the production of force and movement, requires release of calcium from the sarcoplasmic reticulum. Because calcium serves this coupling function in all three types of muscle—cardiac, skeletal, and smooth—it is not surprising that calcium binding proteins have also been identified in these same tissues. Calmodulin occurs in all three muscle types, whereas troponin C has been identified only in skeletal and cardiac muscle. Strong homologies in primary structure exist between calmodulin and troponin C (30,31), suggesting that these two calcium binding proteins had a common evolutionary origin. As will be discussed in the next paragraph, in those muscle types in which both troponin C and calmodulin occur, troponin C selectively mediates calcium effects on the contractile apparatus, whereas calmodulin regulates other reactions of metabolism.

As illustrated in Figure 4, the major contractile proteins found in all three kinds of muscle are actin and myosin (58). The generation of contractile force depends on a cyclic interaction between thick (myosin) and thin (actin) filaments, specifically involving the myosin heads, or crossbridges, and individual actin myofilaments. In the relaxed state of skeletal and cardiac muscle (i.e., in the absence of calcium), a regulatory protein called tropomyosin occupies a position on the thin filament masking the sites at which actin would bind to myosin. A second regulatory protein, troponin, consists of three loosely-associated subunits: troponin T (tropomyosin-binding), troponin I (inhibitory), and troponin C (calcium-binding). Calcium released from the sarcoplasmic reticulum binds to troponin C. The resulting calcium-troponin C complex binds to troponin I, which frees troponin T to interact with tropomyosin. Tropomyosin then rotates away from actin that is able to bind to myosin. The binding of actin to myosin activates myosin ATPase to start the cycling of crossbridges that permits contraction to occur (Figure 5). While the actin-myosin interaction is not well characterized in molecular terms, it does result in the splitting of MgATP by the myosin ATPase, located in the head region of the thick filament. The binding of MgATP to the myosin head is associated with a loose binding (allowing detachment and reattachment) of the crossbridges to actin and the hydrolysis of ATP to ADP plus inorganic phosphate (58). This hydrolysis of MgATP furnishes the energy for muscle contraction. The extent to which contraction is activated (i.e., the amount of force generated) depends on the concentration of ionized calcium attained in the myoplasm.

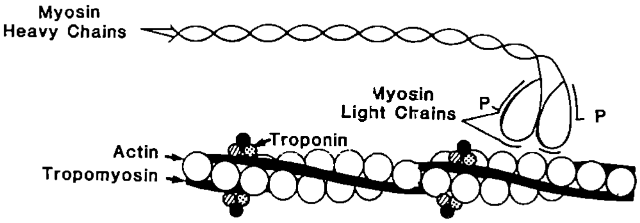


Figure 5. Diagram of the muscle contractile proteins. The phosphorylated light chains are indicated (P), but the exact location of the myosin light chains with respect to the heavy chains is not known. Skeletal, cardiac, and smooth muscle contain actin, myosin, and tropomyosin, but troponin has only been positively identified in skeletal and cardiac muscle. (Modified and reprinted with permission from Adelstein RS. Annu Rev Biochem 1980; 49:921–56).

Contraction that occurs in smooth muscle and in some nonmuscle cells is also mediated by calcium, albeit in response to a chemical rather than electrical stimulus. Also, the calcium message is conveyed not through the calcium-troponin C-tropomyosin interaction as occurs in skeletal muscle, but rather through the enzyme myosin light chain kinase on its being activated by calcium-calmodulin. Myosin light chain kinase catalyzes site-specific phosphorylation of a myosin regulatory subunit (the so-called "light chain"—approximately 20,000 daltons) (59). This chemical alteration and the ensuing conformational change in myosin produce the same end result in smooth muscle as does tropomyosin's conformational change in cardiac and skeletal muscle: there is

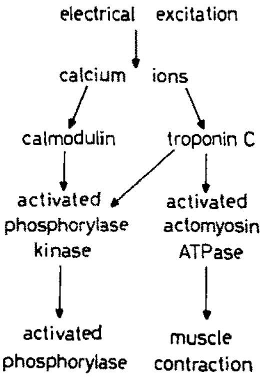


Figure 6. Calcium control of phosphorylase kinase through the combined action of calmodulin (the δ subunit) and troponin C. (Reprinted with permission from Cohen P. Ann NY Acad Sci 1980; 356:151–61).

enhanced binding between myosin and actin, activating myosin ATPase to generate the energy necessary for muscle contraction to occur. In summary, the calcium signal for contraction is transduced by troponin C + tropomyosin in cardiac and skeletal muscle and by calmodulin + myosin light chain kinase in smooth muscle and nonmuscle cells.

In addition to the muscle contraction that occurs when calcium is released from the sarcoplasmic reticulum of skeletal muscle, that same calcium also serves to stimulate the breakdown of glycogen to make glucose available to support the additional ATP production needed for the contractile process. Glycogen phosphorylase and glycogen synthetase control the rates of glycogen degradation and formation, respectively. Because phosphorylation activates glycogen phosphorylase but inhibits glycogen synthetase, simultaneous calcium-dependent phosphorylation of the two enzymes greatly enhances the overall rate of glucose mobilization. Phosphorylation of glycogen phosphorylase to convert it from the inactive (or B) form to the active (A) form is catalyzed by phosphorylase kinase, which contains calmodulin as one of its four different polypeptide subunits and is therefore activated by calcium (60). Conversion of glycogen synthetase from its active (A) to inactive (B) form is also catalyzed by a specific kinase that is calcium-calmodulin-dependent (61). Thus, calcium increases that activate skeletal muscle contraction simultaneously activate glucose mobilization by a second mechanism.

Furthermore, it appears that the regulation of phosphorylase kinase in skeletal muscle can also be mediated by troponin C as well as by calmodulin, as shown in Figure 6. It has been shown that troponin C rather than calmodulin is the predominant calcium-dependent regulator of phosphorylase kinase when the latter is in its inactive/unphosphorylated form. The phosphorylation of phosphorylase kinase is cyclic AMP- rather than calcium-dependent and thus is not biochemically linked to depolarization-induced myoplasmic calcium increases, so the existence of a calcium-dependent activator of unphosphorylated phosphorylase kinase helps to ensure an adequate degree of coupling between glycogenolysis and contractile activity in skeletal muscle (60,62).

Possible Role in Malignant Hyperthermia

Malignant hyperthermia reactions are associated with a sudden increase in the concentration of calcium in the muscle cytoplasm. The defect responsible for this sudden rise in myoplasmic calcium during a malignant hyperthermia reaction has not been identified. Marjanen et al. (63) investigated the possibility that calmodulin may be involved in malignant hyperpyrexia by studying the trifluoperazine-induced inhibition of calmodulin activation of phosphodiesterase, using crude and purified calmodulin preparations from control and malignant hyperthermia susceptible pigs. They found no abnormality in the pattern of either calmodulin activation or trifluoperazine-induced inhibition in malignant hyperthermia muscle. These results have been questioned by Cheah et al. (64), who recorded higher than normal levels of calmodulin in adult malignant hyperthermia susceptible Landrace pigs. Cheah et al. (64) hypothesize that elevated calmodulin levels may be responsible for the elevated phospholipase A_2 activity that they have identified in these pigs. Mitochondria isolated from longissimus dorsi muscle of malignant hyperthermia susceptible pigs contain significantly higher amounts of endogenous calmodulin than do normal mitochondria (65). Cheah suggests that calmodulin could be responsible for the abnormal features of porcine malignant hyperthermia susceptible skeletal muscle mitochondria because it mediates the calcium dependent increases in mitochondrial phospholipase A_2 activity. Further studies demonstrated that when skeletal muscle mitochondria from normal pigs are treated with exogenous calmodulin to elevate the calmodulin level to a level equivalent to the endogenous level of malignant hyperthermia skeletal muscle mitochondria, a calcium-induced uncoupling at 40°C is observed as it is with malignant hyperthermia skeletal muscle mitochondria. This uncoupling is prevented by a low concentration (7 nmole/mg mitochondrial protein) of trifluoperazine. It is believed that inhibition of the calcium induced uncoupling by trifluoperazine is due to the inhibition of the calmodulin-dependent phospholipase A_2 activity (64). Morphologic studies of porcine and human malignant hyperthermia demonstrate large amplitude swelling with disrupted cristae in mitochondria of skeletal muscle after halothane and succinylcholine challenge. This calcium-induced large amplitude swelling from skeletal muscle mitochondria has been attributed to an enhanced calmodulin-dependent calcium-activated phospholipase A_2 activity, because the swelling is prevented by phospholipase A_2 inhibitors (65).

Regulation of Neurotransmitter Release

Several lines of evidence support a role for calmodulin as the predominant receptor for the second messenger calcium that triggers neurotransmitter release from presynaptic neurons (66,67). Calmodulin is present in substantial amount in the vicinity of synaptic vesicles in intact cells, as is a specific calmodulin-activated protein kinase (type II) (68,69). The selectivity order of divalent cations for binding to calmodulin is the same as that for triggering neurotransmitter release in permeabilized or microinjected nerve cells, and addition of trifluoperazine inhibits neurotransmitter release from preparations of isolated nerve cell endings ("synaptosomes") (10,22). The binding of calmodulin to isolated synaptic vesicles containing neurotransmitter is avid and is associated with neurotransmitter release from the vesicles (66). Vesicle-associated substrate proteins for the type II kinase are actively phosphorylated under the same conditions that promote neurotransmitter release, and both have been observed with microinjection of type II kinase into nerve cell terminals (70).

Interaction of Drugs with Calmodulin

Phenothiazines (Antipsychotic Agents)

Antipsychotic drugs of the phenothiazine type, such as chlorpromazine and trifluoperazine, are among the many drugs known to perturb calcium-calmodulin-enzyme interactions (71). As noted earlier, the binding of calcium to calmodulin causes a conformational change crucial to the ability of calmodulin to activate various enzymes. Along with a 5–10% increase in alpha-helical structure (19,37,38,72), this conformational change also exposes hydrophobic sites on the calmodulin molecule (18,34–36). Binding of phenothiazines occurs at these hydrophobic sites and inhibits the interaction of calmodulin with its target enzymes. Interactions between phenothiazines and calmodulin are much weaker in the absence of calcium, supporting the fact that calcium is required to expose the hydrophobic sites where phenothiazines bind (37,38). Norman et al. (73) found a linear relationship between the logarithm of the potency with which phenothiazines antagonize phosphodiesterase activation by calmodulin and the logarithm of their octanol-water partition coefficients. Thus trifluoperazine, penfluridol, and pimozide, which are among the most potent antagonists of calmodulin, are also among the most hydrophobic (73,74). Cross-linking studies show that phenothiazines bind in a middle region of the calmodulin molecule (residues 38–75) and at two regions near the carboxyl end (residues 107–126 and 127–148) (74). Binding of trifluoperazine alters the nuclear magnetic resonance (NMR) spectrum of just a single phenylalanine residue (75), suggesting little interaction of phenothiazine with the aromatic amino acid side chains that are important regions of hydrophobicity in many other proteins. Thus, whereas hydrophobicity may be a major determinant of the anticalmodulin potency of phenothiazines, other factors may also play a role, e.g., there could also be ionic interaction between positively charged functional groups on the phenothiazine ring and negatively charged amino acid side chains (76). Phenothiazine-calmodulin binding can generally be reversed by sequestering calcium with chelating agent (76), but irreversible inactivation of calmodulin can be produced by ultraviolet irradiation of certain phenothiazine species while they are bound to the protein (77). The hydrophobicity of phenothiazines correlates well with their potency for calmodulin antagonism but not with their antipsychotic potencies (73,74). This finding is not surprising because phenothiazines are known to be poorly selective antagonists of calmodulin except in simplified in vitro systems. Phenothiazines can produce changes in specific neuronal functions, including blockade of nerve impulses and of the uptake and release of neurotransmitters, at concentrations well below those required to inhibit calmodulin actions in vitro (78).

Anesthetics

In 1974, Price (79) demonstrated the ability of halothane to decrease contractile force in isolated papillary muscle and showed also that increasing the ionized calcium concentration of the bathing medium could reverse the negative inotropic effect. The latter finding has been exploited clinically by the use of intravenous calcium chloride to partially counteract myocardial depression due to halogenated volatile anesthetics (80). However, the underlying assumption that halothane exerts its negative inotropic effect at least in part through inhibition of calcium-mediated events in excitation-contraction coupling has been difficult to address experimentally in intact systems because anesthetics and calcium each have multiple intracellular actions. In fact, only recently has there begun to appear information on the direct effects of any anesthetic(s) on intracellular calcium signaling events in any specific tissue.

Isolated cardiac fibers in which membrane-associated activities were selectively obliterated by detergent treatment were used to demonstrate that halogenated volatile anesthetics increase the ionized calcium concentration required to activate the contractile apparatus (81). One of several possible explanations for this finding is that halothane alters the binding of troponin to either calcium or tropomyosin, although others have reported that the binding of calcium to troponin is unaffected by halothane (82). This diminished calcium sensitivity of troponin and/or other contraction-activating cardiac myofibrillar proteins produced by the halogenated anesthetics could very definitely contribute to the negative inotropic effects so prominent in the clinical usage of these agents. However, in accounting overall for the myocardial depressant effects of volatile anesthetics, the relative importance of direct actions on myofibrils, such as those just described, vis a vis other possibilities, such as changes in membrane-regulated calcium fluxes that alter myoplasmic calcium levels (83,84), remains to be determined.

Data from the laboratory of one of us (K.C.W.) suggest that both local and general anesthetics inhibit calmodulin's ability to activate myosin light chain kinase (MLCK) of smooth muscle. In an in vitro test system consisting of myosin and MLCK purified from turkey gizzard smooth muscle, along with added calmodulin and calcium, the MLCK-catalyzed, calcium- and calmodulin-dependent phosphorylation of myosin (an essential step in contractile activation of smooth muscle—see section on Calmodulin and Troponin C in Muscle Contraction and Metabolism) was inhibited by local anesthetics in the order of potency tetracaine > bupivacaine > lidocaine (85). This inhibitory effect of local anesthetics on MLCK activity was only partly reversed by raising the free calcium concentration from 1×10^{-5} M to 2×10^{-4} M, whereas MLCK activity was completely restored by raising the calmodulin concentration from 1×10^{-7} M to 6×10^{-7} M (Nosaka S, Kamaya H, Ueda I, Wong KC, unpublished data). Furthermore, these investigators have also found that halothane and isoflurane exhibited weak MLCK-inhibiting effects that were dependent on the presence of calmodulin (85; Wong KC, unpublished data).

It seems likely that the inhibitory action of local anesthetics is caused by their interaction with the hydrophobic domain of calmodulin, because binding of local anesthetics to calmodulin occurs through the aromatic portion of the drug molecule. Within a series of local anesthetics (e.g., lidocaine, tetracaine, and dibucaine) there is a linear relation between the logarithms of the octanol-water partition coefficients and the median inhibitory concentrations for calmodulin activation of phosphodiesterase or MLCK (86). Local anesthetics prevent the binding of calmodulin to the erythrocyte membrane, with corresponding inhibition of calcium-stimulated ATPase activity (87). Procaine, lidocaine, tetracaine, and dibucaine also inhibit the calcium pump of sarcoplasmic reticulum (88). Phosphodiesterase activation by calmodulin is inhibited also by propranolol (89). Because the associated binding is non-stereospecific and occurs at relatively high drug concentration, it presumably reflects local anesthetic rather than β-adrenergic antagonistic actions of propranolol.

Calcium Channel Blockers

In vitro, these drugs also bind to the activated form of calmodulin (the calcium-calmodulin complex) and prevent its interaction with target enzymes. The four main groups of calcium channel blockers—dihydropyridines, phenylalkylamines, benzothiazepines, and diphenylalkylamines—recognize different, distinct sites on the oligomeric channel protein (90). Felodipine (91–93), prenylamine (94), bepridil, and flunarizine (95) interact with calmodulin in vitro. Agre et al. (96) concluded that bepridil and cetiedil interact with calmodulin rather than with the calcium channel(s) in the erythrocyte membrane. Because no clear evidence has been put forward for direct involvement of calmodulin in the pharmacological effects of calcium channel blockers, more work is needed to explore the possibility that calcium channel function may be modulated by calmodulin-dependent protein kinase or phosphatase activity (97,98).

Conclusions and Future Directions

As detailed throughout this article, calcium regulates many cellular reactions and processes, in some cases by mechanisms not yet fully understood. Calmodulin, which plays a central role as both a receptor for calcium and a mediator of its effects, deserves continued intensive study. Of considerable importance to anesthesiology would be further work on the following questions, especially as they pertain to the function of calmodulin in nerve and muscle: 1) What is the complete roster of intracellular processes that are calcium- and calmodulin-dependent? 2) What are the detailed interactions between the calcium and cyclic AMP messenger systems, and among different intracellular mediators of calcium effects, such as calmodulin and protein kinase C? 3) How do anesthetics affect the regulation of ionized calcium levels in (intra)cellular compartments? 4) What are the effects of anesthetics on calmodulin's ability to mediate calcium-dependent cellular activities? 5) Are there non-anesthetic drugs able to specifically and reversibly interact with calmodulin and alter its ability to bind calcium or its target enzymes?

Increased knowledge in these areas will improve our understanding of basic mechanisms involved in calcium's ability to regulate cellular activities. Such an understanding offers the potential for predicting the influence of drugs and other anesthetic interventions on important calcium-dependent reactions and processes. Eventually, we may be able to manipulate, with potency and specificity, various elements of the calcium messenger system, much as is now possible for other first (e.g., adrenergic) and second (e.g., cyclic AMP) messenger systems. That capability would provide the anesthesiologist with a new dimension of control over many critical physiological functions.

We thank John Tseng for assistance in literature review and Shelly McCaffrey for secretarial support.

References

1. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J Physiol 1883–84;4:29–42.
2. Heilbrunn LV, Wiercinski FJ. The action of various cations on muscle protoplasm. J Cell Comp Physiol 1947;29:15–32.
3. Rasmussen H. The calcium messenger system. N Engl J Med 1986;314:1094–101, 1164–70.
4. England PJ. Intracellular calcium receptor mechanisms. Br Med Bull 1986;42:375–83.
5. Kretsinger RH. Calcium binding proteins. Ann Rev Biochem 1976;45:239–66.
6. Maze M. Clinical implications of membrane receptor functions in anesthesia. Anesthesiology 1981;55:160–71.
7. Wolff DJ, Siegel FL. Purification of a calcium-binding phosphoprotein from pig brain. J Biol Chem 1972;247:4180–5.
8. Kakiuchi S, Yamazaki R. Calcium dependent phosphodiesterase activity and its activating factor (PAF) from brain. Biochem Biophys Res Commun 1970;41:1104–10.
9. Cheung WY. Cyclic 3',5' nucleotide phosphodiesterase: demonstration of an activator. Biochem Biophys Res Commun 1970;38:533–8.
10. Teo TS, Wang JH. Mechanism of activation of cyclic adenosine 3', 5'-monophosphate phosphodiesterase from bovine heart by calcium ion. J Biochem 1973;248:5950–5.
11. Wolff DJ, Brostrom CO. Properties and functions of the calcium-dependent regulator protein. Adv Cyclic Nucleotide Protein Phosphorylation Res 1979;11:27–88.
12. Cheung WY, Lynch TJ, Wallace RW. An endogenous Ca^{++}-dependent activator proteins of brain adenylate cyclase and cyclic nucleotide phosphodiesterase. Adv Cyclic Nucleotide Protein Phosphorylation Res 1978;9:233–51.
13. Manalan AS, Klee CB. Calmodulin. Adv Cyclic Nucleotide Protein Phosphorylation Res 1984;18:227–78.
14. Brostrom CO, Huang YC, Brechenridge B, Wolff DJ. Identification of a calcium binding protein as a calcium-dependent regulator of brain adenylate cyclase. Proc Natl Acad Sci USA 1975;72:64–8.
15. Jarrett HW, Penniston JT. Partial purification of the $Ca^{++} - Mg^{++}$ ATPase activator from human erythrocytes: its similarity to the activator of 3', 5'-cyclic nucleotide phosphodiesterase. Biochem Biophys Res Commun 1977;77:1210–6.
16. Gopinath RM, Vincenzi FF. Phosphodiesterase protein activator mimics red blood cells cytoplasmic activator of (Ca^{++}, Mg^{++}) ATPase. Biochem Biophys Res Commun 1977; 77:1203–9.
17. Smoake JA, Song SY, Cheung WY. Cyclic 3',5'-nucleotide phosphodiesterase: distribution and developmental changes of the enzyme and its protein activator in mammalian tissues and cells. Biochim Biophys Acta 1974;341:402–11.
18. Klee CB. Conformational transition accompanying the binding of Ca^{++} to the protein activator of 3',5'-cyclic adenosine monophosphate phosphodiesterase. Biochemistry 1977;16: 1017–24.
19. Lin YM, Liu YP, Cheung WY. Cyclic 3',5'-nucleotide phosphodiesterase. Purification, characterization and active form of the protein activator from bovine brain. J Biol Chem 1974; 249:4943–54.
20. Kuo ICY, Coffee CJ. Purification and characterization of a troponin C-like protein from bovine adrenal medulla. J Biol Chem 1976;251:1603–9.
21. Dedman JR, Potter JD, Jackson RL, Johnson JD, Means AR. Physicochemical properties of rat testis Ca^{++} dependent regulator protein of cyclic nucleotide phosphodiesterase: relationship of Ca^{++} binding, conformational changes and phosphodiesterase activity. J Biol Chem 1977;252:8415–22.
22. Childers SR, Siegel FL. Isolation and purification of a calcium-binding protein from electroplax of *Electrophorus electricus*. Biochim Biophys Acta 1975;405:99–108.
23. Egrie JC, Campbell JA, Flangas AL, Siegel FL. Regional, cellular and subcellular distribution of calcium-activated cyclic nucleotide phosphodiesterase and calcium-dependent regulator in porcine brain. J Neurochem 1977.28:1207–13.
24. Kakiuchi S, Yamazaki R, Teshima Y, et al. Membrane-bound protein modulator and phosphodiesterase. Adv Cyclic Nucleotide Protein Phosphorylation Res 1978;9:253–63.
25. Brostrom CO, Brostrom MA, Wolff DJ. Calcium dependent adenylate cyclase from rat cerebral cortex: reversible activation by sodium fluoride. J Biol Chem 1977;252:5677–85.
26. Campbell KP, MacLennan DH, Jorgensen AO. Staining of the Ca^{2+}-binding proteins, calsequestrin, calmodulin, troponin C, and S-100, with the cationic carbocyanine dye "Stains-all." J Biol Chem 1983;258:11267–73.
27. Welsh MJ, Dedman JR, Brinkley BR, Means AR. Calcium-dependent regulator protein: localization in mitotic apparatus of eukaryotic cells. Proc Natl Acad Sci USA 1978;75:1867–71.
28. Harper JF, Cheung WY, Wallace RW, Huang HL, Levine SN, Steiner AL. Localization of calmodulin in rat tissues. Proc Natl Acad Sci USA 1980;77:366–70.
29. Klee CB, Vanaman TC. Calmodulin. Adv Protein Chem 1982; 35:213–321.

30. Vanaman TC, Sharief F, Watterson DM. Structural homology between brain modulator protein and muscle Tn-C. In: Wasserman RN, Corradino RA, Carafoli E, et al., eds. Calcium Binding Proteins and Calcium Functions. New York: Elsevier/North Holland, 1977:457–72.
31. Watterson DM, Sharief F, Vanaman TC. The complete amino acid sequence Ca^{++}-dependent modulator protein (calmodulin) of bovine brain. J Biol Chem 1980;255:462–75.
32. Cheung WY. Calmodulin: an overview. Fed Proc 1982;41: 2253–7.
33. Cheung WY. Biologic functions of calmodulin. Harvey Lect 1985;79:173–216.
34. Wolff DJ, Poirier PG, Brostrom CO, Brostrom MA. Divalent cation binding properties of bovine brain Ca^{++}-dependent regulator protein. J Biol Chem 1977;252:4108–17.
35. Walsh M, Stevens FC. Chemical modifications studies on the Ca^{++} dependent protein modulator of cyclic nucleotide phosphodiesterase. Biochemistry 1977;16:2742–9.
36. Liu YP, Cheung WY. Cyclic 3′, 5′-nucleotide phosphodiesterase: Ca^{2+} confers more helical conformation to the protein activator. J Biol Chem 1976;251:4193–8.
37. LaPorte DC, Wierman BM, Storm DR. Calcium-induced exposure of a hydrophobic surface on calmodulin. Biochemistry 1980;19:3814–9.
38. Tanaka T, Hidaka H. Hydrophobic regions function in calmodulin-enzyme interactions. J Biol Chem 1980;255:11078–80.
39. Lynch TJ, Tallant EA, Cheung WY. Ca^{++}-dependent formation of brain adenylate cyclase-protein activator complex. Biochem Biophys Res Commun 1976;68:616–25.
40. Cheung WY. Calmodulin plays a pivotal role in cellular regulation. Science 1980;207:19–27.
41. Chao SH, Suzuki Y, Zysk JR, Cheung WY. Activation of calmodulin by various metal cations as a function of ionic radius. Mol Pharmacol 1984;26:75–82.
42. Nicholls DG. Intracellular calcium homeostasis. Br Med Bull 1986;42:353–8.
43. Putney JW Jr. Calcium-mobilizing receptors. Trends Pharmacol Sci 1987;8:481–6.
44. Berridge MJ, Irvine RF. Inositol trisphosphate, a novel second messenger in cellular signal transduction. Nature 1984; 312:315–21.
45. Berridge MJ. Inositol trisphosphate and diacylglycerol: two interacting second messengers. Annu Rev Biochem 1987; 56:159–93.
46. Exton JH. Role of phosphoinositides in the regulation of liver function. Hepatology 1988;8:152–66.
47. Nishizuka Y. Studies and perspectives of protein kinase C. Science 1986;233:305–12.
48. Alkon DL, Rasmussen H. A spatial-temporal model of cell activation. Science 1988;239:998–1005.
49. Nathanson JA. Cyclic nucleotides and nervous system function. Physiol Rev 1977;57:157–256.
50. Schwabe U, Ohga Y, Daly JW. The role of calcium in the regulation of cyclic nucleotide levels in brain slices of rat and guinea pig. Naunyn Schmiedebergs Arch Pharmacol 1978; 302:141–51.
51. Cheung WY, Bradham LS, Lynch TJ, et al. Protein activator of cyclic 3′-5′ nucleotide phosphodiesterase of bovine or rat brain also activates its adenylate cyclase. Biochem Biophys Res Commun 1975;66:1055–62.
52. Cheung WY. Role of calmodulin in brain function. Prog Brain Res 1982;56:237–53.
53. Piascik MT, Wisler PL, Johnson CL, Potter JD. Ca^{2+}-dependent regulation of guinea pig brain adenylate cyclase. J Biol Chem 1980;255:4176–81.
54. Schatzmann HJ. In: Carafoli E, ed. Membrane Transport of Calcium. London: Academic Press, 1982:41–108.
55. Carafoli E. Intracellular calcium homeostasis. Annu Rev Biochem 1987;56:395–433.
56. Larsen FL, Vincenzi FF. Calcium transport across the plasma membrane: stimulation by calmodulin. Science 1979;204:306–8.
57. Carafoli E. Calmodulin in the membrane transport of Ca^{++}. Cell Calcium 1981;2:353–63.
58. Rusy BF, Komai H. Anesthetic depression of myocardial contractility: a review of possible mechanisms. Anesthesiology 1987;67:745–66.
59. Adelstein RS, Klee CB. Smooth muscle myosin light chain kinase. In: WY Cheung, ed. Calcium and Cell Function, Vol. 1. New York: Academic Press, 1980:457–72.
60. Cohen P, Klee CB, Picton C, Shenolikar S. Calcium control of muscle phosphorylase kinase through the combined action of calmodulin and troponin. Ann NY Acad Sci 1980;356:151–61.
61. Payne ME, Soderling TR. Calmodulin-dependent glycogen synthase kinase. J Biol Chem 1980;255:8054–6.
62. Posner JB, Stern R, Krebs EG. Effects of electrical stimulation and epinephrine on muscle phosphorylase, phosphorylase b kinase, and adenosine 3′, 5′-phosphate. J Biol Chem 1965; 240:982–5.
63. Marjanen LA, Collins SP, Denborough MA. Calmodulin and malignant hyperpyrexia. Biochem Med 1984;32:283–7.
64. Cheah KS. Skeletal-muscle mitochondria and phospholipase A_2 in malignant hyperthermia. Biochem Soc Trans 1984; 12:358–60.
65. Cheah KS, Cheah AM. Mitochondrial calcium transport and calcium-activated phospholipase in porcine malignant hyperthermia. Biochim Biophys Acta 1981;634:70–84.
66. DeLorenzo RJ. Role of calmodulin in neurotransmitter release and synaptic function. Ann NY Acad Sci 1980;356:92–109.
67. Augustine GJ, Charlton MP, Smith SJ. Calcium action in synaptic transmitter release. Ann Rev Neurosci 1987;10:633–93.
68. Moskowitz N, Schook W, Beckenstein K, Puszkin S. Preliminary characterization of synaptic vesicle calmodulin interaction. Brain Res 1983;263:243–50.
69. Nairn AC, Hemmings HC Jr, Greengard P. Protein kinases in the brain. Annu Rev Biochem 1985;54:931–76.
70. Llinas R, McGuinness TL, Leonard CS, Sugimori M, Greengard P. Intraterminal injection of synapsin I or calcium-calmodulin-dependent protein kinase II alters neurotransmitter release at the squid giant synapse. Proc Natl Acad Sci USA 1985;82:3035–9.
71. Levin RM, Weiss B. Specificity of the binding of trifluoperazine to the calcium-dependent activator of phosphodiesterase and to a series of other calcium-binding proteins. Biochim Biophys Acta 1978;540:197–204.
72. Klee CB, Crouch TH, Richman PG. Calmodulin. Annu Rev Biochem 1980;49:489–515.
73. Norman JA, Drummond AH, Moser P. Inhibition of calcium-dependent regulator-stimulated phosphodiesterase activity by neuroleptic drugs is unrelated to their clinical efficacy. Mol Pharmacol 1979;16:1089–94.
74. Roufogalis BD. Comparative studies on the membrane actions of depressant drugs: the role of lipophilicity in inhibition of brain sodium and potassium-stimulated ATPase. J Neurochem 1975;24:51–61.
75. Klevit RE, Levine BA, Williams RJP. A study of calmodulin and its interaction with trifluoperazine by high resolution ^1H NMR spectroscopy. FEBS Lett 1981;123:25–9.
76. Weiss B, Levin RM. Mechanism for selectively inhibiting the activation of cyclic nucleotide phosphodiesterase and adenyl-

ate cyclase by antipsychotic agents. Adv Cyclic Nucleotide Protein Phosphorylation Res 1978;9:285–303.

77. Prozialeck WC, Cimino M, Weiss B. Photoaffinity labeling of calmodulin by phenothiazine antipsychotics. Mol Pharmacol 1981;19:264–9.
78. Phillis JW, Wu PH. Phenothiazines inhibit adenosine uptake by rat brain synaptosomes. Can J Physiol Pharmacol 1981; 59:1108–10.
79. Price HL. Calcium reverses myocardial depression caused by halothane. Anesthesiology 1974;41:576–9.
80. Shapiro N, Schaff HV, White RD, et al. Hemodynamic effects of calcium chloride injection following cardiopulmonary bypass: response to bolus injection and continuous infusion. Ann Thorac Surg 1984;37:133–40.
81. Murat I, Ventura-Clapier R, Vassort G. Halothane, enflurane, and isoflurane decrease calcium sensitivity and maximal force in detergent-treated rat cardiac fibers. Anesthesiology 1988; 69:892–9.
82. Casella ES, Blanck TJJ. The effect of halothane on the binding of calcium by cardiac troponin C (abstr). Biophys J 1988;53: 583a.
83. Bosnjak ZJ, Kampine JP. Effects of halothane on transmembrane potentials, Ca^{2+} transients and papillary muscle tension in the cat. Am J Physiol 1986;251:H374–81.
84. Wheeler DM, Rice RT, Hansford RG, Lakatta EG. The effect of halothane on the free intracellular calcium concentration of isolated rat heart cells. Anesthesiology 1988;69:578–83.
85. Nosaka S, Kamaya H, Wong KC. Local anesthetic toxicity on vascular muscle contractility. 1. Myosin and calmodulin-dependent myosin light chain kinase (abstr). Anesth Analg 1988;67:S158.
86. Tanaka T, Hidaka H. Interaction of local anesthetics with calmodulin. Biochem Biophys Res Commun 1981;101:447–53.
87. Roufagolis BD. Specificity of trifluoperazine and related phenothiazines for calcium-binding proteins. In: Cheung WY, ed. Calcium and Cell Function, Vol. 3. New York: Academic Press, 1982:127–75.
88. Suko J, Winkler F, Scharinger B, Hillmann G. Aspects of the mechanism of action of local anesthetics on the sarcoplasmic reticulum of skeletal muscle. Biochim Biophys Acta 1976; 443:571–86.
89. Volpi M, Sha'afi RI, Epstein PM, Andrenyak DM, Feinstein MB. Local anesthetics, mepacrine, and propranolol are antagonists of calmodulin. Proc Natl Acad Sci USA 1981;78:795–9.
90. Winkler MA, DeWitt LM, Cheung WY. Calmodulin and calcium channel blockers. Hypertension 1987;9:217–23.
91. Bostrom SL, Ljung B, Mardh S, Forsen S, Thulin E. Interactions of the antihypertensive drug felodipine with calmodulin. Nature 1981;292:777–8.
92. Johnson JD. Allosteric interaction among drug binding sites on calmodulin. Biochem Biophys Res Commun 1983;112:787–93.
93. Mills JS, Bailey BL, Johnson JD. Cooperativity among calmodulin's binding sites. Biochemistry 1985;24:4897–902.
94. Hidaka H, Yamaki T, Naka M, Tanaka T, Hayashi H, Kobayashi R. Calcium regulated modulator protein interacting agents inhibit smooth muscle Ca^{2+} stimulated protein kinase. Mol Pharmacol 1980;17:66–72.
95. Lugnier C, Follenius A, Gerard D, Stoclet JC. Bepridil and flunarizine as calmodulin inhibitors. Eur J Pharmacol 1984; 98:157–8.
96. Agre P, Virshup D, Bennet V. Bepridil and cetiedil: vasodilators which inhibit Ca^{2+}-dependent calmodulin interactions with erythrocyte membranes. J Clin Invest 1984;74:812–20.
97. Bkaily G, Sperelakis N. Calmodulin is required for a full activation of the calcium slow channels in heart cells. J Cyclic Nucleotide Protein Phosphor Res 1986;11:25–34.
98. Asano M, Hidaka H. Biopharmacological properties of naphthalene sulfonamides as potent calmodulin antagonists. In: Cheung WY, ed. Calcium and Cell Functions, Vol. 4. New York: Academic Press, 1984:123–64.

ANESTH ANALG 113
1989;69:113–5

Clinical Reports

Back Pain Following Epidurally Administered Nesacaine-MPF

Eugene E. Fibuch, MD, and Susan E. Opper, MD

Key Words: ANESTHETICS, LOCAL—2-chloroprocaine. ANESTHETIC TECHNIQUES, EPIDURAL—back pain.

Since 1980, reports have appeared describing prolonged neurologic deficits following presumed accidental intrathecal administration of 2-chloroprocaine (2-CP) (1–4). The 2-chloroprocaine solutions that were used in these reports of neurologic deficit presumably contained, in addition to the 2-CP HCl, sodium bisulfite (0.2%), and sodium chloride (4). Methylparaben (0.1%) was removed in 1956 from the 3% solution of 2-CP. In 1964, the 2% and 3% solutions of 2-CP without methylparaben were marketed for caudal and epidural administration as Nesacaine-CE (5).

The sodium bisulfite (0.2%) in 2-CP solutions prevents the oxidation of 2-CP and lowers the pH to approximately 3.0. Controversy centered on whether the reported neurologic deficits were due to the antioxidant (sodium bisulfite), the low pH, or the 2-CP itself (6). Covino suggested that a combination of a low pH and the presence of sodium bisulfite was probably responsible for the neurologic deficits (7).

In October of 1987, the Astra Corporation (Astra Pharmaceutical Products, Inc., Westborough, Mass.), in an effort to eliminate the bisulfite in the 2% and 3% concentrations of 2-chloroprocaine, began marketing for general use a new formulation of 2-CP for epidural and caudal use labeled as Nesacaine-MPF (methylparaben free 2-chloroprocaine). In place of the bisulfite, the new formulation contained disodium EDTA 0.1 mg/mL (ethylenediaminetetraacetic acid). The Nesacaine-CE preparation also contains an EDTA preparation (calcium disodium EDTA) (8). The following case reports from our institution suggest the possibility that this new formulation may result in significant patient discomfort as a result of muscular back pain following the injection of Nesacaine-MPF into the lumbar epidural space. To our knowledge, the occurrence of localized back pain using this preparation of 2-CP has not been reported.

Clinical Experience

Beginning in April of 1988, we began noticing a portion of our ambulatory surgical patients who complained of localized paralumbar muscle pain in the recovery room. These patients had been given lumbar epidural anesthesia using either the 2% or 3% Nesacaine-MPF. The muscle pain lasted for approximately 24 hr postoperatively and, in all patients, required the use of narcotic analgesics and, in some instances, orally administered muscle relaxants for pain relief. To date, we have observed this phenomenon in 8 of 20 patients who have been given Nesacaine-MPF (Table 1) for an incidence of 40%.

A strikingly similar scenario appeared to be evident in each patient. All were given the Nesacaine-MPF epidurally, 7 patients were given the 3%, and 1 patient the 2% concentration. In only one of these patients was epinephrine added. No attempt was made to alkalinize these solutions. The epidural anesthetic in this group of patients was performed by various staff anesthesiologists using a 17-gauge Tuohy needle and the loss of resistance technique. The local anesthetic solution was injected into the lumbar epidural space at either the L_{3-4} or L_{4-5} interspace following the usual skin preparation with a betadine solution and sterile draping. There was no evidence of cerebral spinal fluid or blood on aspiration, and no paraesthesias occurred during the nee-

---

Received from the Department of Anesthesiology, St. Luke's Hospital of Kansas City, 44th & Wornall Road, Kansas City, Missouri. Accepted for publication February 8, 1989.

Address correspondence to Dr. Fibuch, Department of Anesthesiology, St. Luke's Hospital of Kansas City, 44th & Wornall Rd., Kansas City, MC 64111.

©1989 by the International Anesthesia Research Society

Table 1. Case Summary April–May 1988

Patient	1	2	3	4	5	6	7	8
Age (yrs)	27	50	51	29	36	35	28	30
ASA Physical Status	1	1	2	1	1	1	1	1
Surgical Procedure	A	A	A	A	A	H	A	I
Initial Epidural Dose (mL)	25	30	27	27	32	28	26	23
Total Epidural Dose (mL)	40	30	27	27	32	28	32	23
Surgical Duration (min)	76	75	85	63	90	45	80	90
Epidural Catheter	+	+	+	+	+	+	+	−
Satisfactory Anesthesia	+	+	+	+	+	+	+	+
Technical Problems	−	−	−	−	−	−	−	−
Anesthesiologist	WH	JJ	EF	JM	SO	EF	MH	MH

A = arthroscopy, H = hysteroscopy, I = inguinal hernia repair, + = Yes, − = No.

dle placements. There were no marked differences in total volume of 2-CP used, duration of surgery, or technical complications in the 20 patients given the Nesacaine-MPF. In all cases, the anesthetic was successfully completed, only to have the patient experience the onset of localized back pain as the sensory blockade wore off.

The pain was described by the patients as being intense and localized to the lower back. The pain was associated with observable muscle spasm and tenderness upon physical examination in some of the patients. There was no evidence of muscle weakness, sensory deficit, or muscular discoordination of the lower extremities upon examination in the recovery room or during a structured telephone interview format 24 hr postoperative in the eight patients who experienced the muscle pain. Review of 12 months of anesthetic records of patients who received epidural anesthesia for a variety of ambulatory surgical procedures did not reveal a single case of localized paralumbar muscle pain using other local anesthetic preparations, including the previously available 2-CP preparation (2% and 3% Nesacaine-CE containing 0.07% sodium bisulfite and 0.1% calcium disodium EDTA). This retrospective chart review included not only the anesthetic record and recovery room record but, also, the record of a 24-hr postoperative structured telephone interview, which all of our ambulatory patients receive.

Table 2. Nesacaine 3%-MPF Lot Analyses

	Expected Range	Lot #710029*	Lot #712126†
Chloroprocaine HCl mg/mL	28.5–31.5	30 5	30.7
CABA %‡	<3	0 21	0.26
Disodium EDTA mg/mL	0.100–0.122	0 107	0.111
Sodium (mg/mL)	1.18–1.14	1.27	1.23
Color	clear	clear	clear
Precipitation	none	none	none
pH	2.7–4.0	3.5	3.5
Sodium Bisulfite	none	none	none

*Elliot Hospital, Manchester, NH 03103. †ST. Luke's Hospital, Kansas City, Mo 64111. ‡4-Amino-2-Chlorobenzoic Acid.

Discussion

After the postoperative problems that some of our patients were having with the Nesacaine-MPF, the manufacturer was contacted and the lot number used in our institution (#712126) was returned for analysis. Prior to our report, another institution (personal communication—L. Hood, MD; Elliot Hospital, Manchester, NH 03103) reported to Astra Pharmaceutical that some of their patients were experiencing paralumbar muscle pain following the use of the Nesacaine-MPF formulation. This institution used a different lot number (#710029). Table 2 lists the results of the analyses of these two lots of Nesacaine-MPF. Chemical analysis and visual inspection by the manufacturer of the returned ampuls of Nesacaine-MPF were within normal limits.

The question of muscle spasm and pain located in the paralumbar muscle bed in approximately 40% of our patients given the Nesacaine-MPF raises a number of questions. Could it be that there was a technical problem in the administration of the anesthetic (i.e., multiple subcutaneous and intramuscular injections of Nesacaine-MPF) prior to the placement of the epidural needle resulting in muscle damage or irritation? In no instance could we document this, and the fact that multiple anesthesiologists were having the same problem would suggest that localized muscle trauma did not play a role.

Could the new formulation be irritating in some manner to small non-myelinated nerves within the epidural space, triggering a muscle reflex spasm? This is unlikely since we could not document in our patients any suggestion of small fiber dysfunction such as autonomic dysfunction, radicular pain, or dysesthesia either in the early recovery period or 24 hr postoperatively.

Could the 2-chloroprocaine be causing the muscle pain? This also is unlikely since we could not demonstrate in a retrospective review over the last 12 months the occurrence of this syndrome using the old 2-CP formulation or any other local anesthetic preparation; however, the role of 2-CP diffusing through vertebral foramina into the muscle bed causing a localized myotoxicity cannot be ruled out.

Finally, the possible role of disodium EDTA must be considered. In animal preparations, disodium EDTA causes hypocalcemic tetany when administered rapidly intravenously apparently due to binding of tissue calcium; however, the calcium salt of disodium EDTA does not cause this reaction (9). Nesacaine-CE formulations contained the calcium-disodium EDTA, whereas the Nesacaine-MPF contains the disodium EDTA (8). The sodium salts of EDTA are active chelating agents of heavy metals. The expected binding of calcium, acutely, could cause a lowering of tissue calcium and thus muscle spasm. We speculate that in some of our patients there may have been a rapid uptake of Nesacaine-MPF into the lumbar muscle bed either by local diffusion or movement along neural tracts. The binding of tissue calcium may have triggered localized severe muscle pain.

We have not observed localized paralumbar muscle pain in our obstetrical patients who received Nesacaine-MPF for epidural anesthesia during this same time period. The lack of early ambulation and the greater use of narcotic analgesia in the early postoperative period in obstetrical patients may be masking the occurrence of muscle pain.

We believe further investigation is warranted and that the anesthesia community should be aware of the potential problem with the new formulation of 2% and 3% Nesacaine-MPF.

In summary, we observed a 40% incidence of paralumbar muscle pain and spasm without evidence of neurologic deficit in ambulatory surgical patients undergoing lumbar epidural anesthesia using a preparation of 2-chloroprocaine labeled as Nesacaine-MPF. The cause of the muscle pain and spasm may be related to the addition of disodium EDTA to the 2-chloroprocaine solutions.

References

1. Ravindran RS, Bond VK, Tasch MD, Gupta CD, Luerssen TG. Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 1980;59:447–51.
2. Reisner LS, Hochman BN, Plumer MH. Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesth Analg 1980;59:452–54.
3. Covino BG, Marx GF, Finster M. Prolonged sensory/motor deficits following inadvertent spinal anesthesia. Anesth Analg 1980;59:399–400.
4. Moore DC, Spierdijk J, VanKleef JD, Coleman RL, Love GF. Chloroprocaine neurotoxicity: four additional cases. Anesth Analg 1982;61:155–9.
5. Riggi SJ. Chloroprocaine: Neurotoxicity and formulations in perspective (letter to editor). Anesth Analg 1982;61:715–6.
6. DeJong R. The chloroprocaine controversy. Am J Obst Gyn 1981;140:237–9.
7. Covino BG. Recent advances in local anaesthesia. Can Anaesth Soc J 1986;33:55–8.
8. Personal Communication, Astra Pharmaceutical Products, Inc., 1988.
9. Goodman AG, Goodman LS, Gilman A. The pharmacological basis of therapeutics, 6th edition. New York: MacMillan Publishing Company, 1980:1620–1.

Airway Obstruction Caused by a Kinked Hi-Lo Jet^R Endotracheal Tube during High Frequency Jet Ventilation

David H. Wilks, MD, William C. Tullock, MD, and Miroslav Klain, MD, PhD

Key Words: EQUIPMENT—endotracheal tubes. COMPLICATIONS—tracheal tube obstruction.

An obstructed endotracheal tube represents an acute, critical complication. Causes of obstruction are varied and include mucous plugs, plastic sheared from stylets, herniating cuffs of endotracheal tubes, and collapsed and kinked tubes (1). We report an obstruction that developed in a Hi-Lo Jet^R endotracheal tube during high frequency jet ventilation (HFJV) in a patient undergoing extracorporeal shock-wave lithotripsy (ESWL). The location of the obstruction affected the HFJV in an unusual manner not previously documented.

Case Report

A healthy 32-year-old man with renal calculi was admitted for ESWL. Past medical history, physical examination, and laboratory data including a chest radiogram and electrocardiogram (ECG) were unremarkable.

The patient was brought to the ESWL suite unpremedicated. Monitors included ECG, esophageal stethoscope, pulse oximeter, and a noninvasive blood pressure monitor. With the patient on a litter, anesthesia was induced with thiopental plus succinylcholine to facilitate endotracheal intubation with an 8.0 mm ID Hi-Lo Jet^R (National Catheter Company, Argyle, NY) endotracheal tube. Correct position of the endotracheal tube was confirmed by auscultation of bilateral breath sounds during manual ventilation. Anesthesia was maintained with nitrous oxide and oxygen, N_2O/O_2 60/40%. Vecuronium, 6 mg iv, was administered to maintain muscle relaxation. Arterial oxygen saturation (SaO_2) was 99%.

The patient was placed in the gantry seat of the lithotripter. This seat holds the patient in a semi-reclining (lawn chair) position. The jet gas delivery lumen of the Hi-Lo Jet^R tube was connected to an Acutronic 1000^R (Acutronic, Jona/Rappeswil, Switzerland) ventilator, and ventilation was begun with an inspiratory time of 30%, a driving pressure of 1.7 bar, and a respiratory frequency of 100 cycles/min. The lumen of the Hi-Lo Jet^R tube for airway pressure measurement was not connected. The main lumen of the endotracheal tube remained connected to the anesthetic circle system with the pressure relief valve fully open to allow scavenging of exhaled gases. Breath sounds were present and equal bilaterally.

The patient was submerged in the water bath to the nipple line. Auscultation of the chest then revealed breath sounds to be absent bilaterally, even though the jet ventilator appeared to be delivering gases. SaO_2 decreased to 85% as shown by the pulse oximeter. Jet ventilation was discontinued, and manual ventilation was attempted with the conventional anesthesia circuit and 100% oxygen. In spite of high ventilatory pressures (80 cm H_2O), the tidal volume was judged clinically to be inadequate, but sufficient oxygen was delivered to return the SaO_2 to 100%. Attempts to pass a suction catheter through the endotracheal tube were unsuccessful, and it was concluded that the endotracheal tube had kinked. The gantry seat's headrest was repositioned to extend the patient's neck without significant improvement in ventilation, and the patient was expeditiously removed from the water bath and placed on a litter. The Hi-Lo Jet^R endotracheal tube was removed, and an armored endotracheal tube inserted. Conventional ventilation through this tube was easily accomplished, and the rest of the procedure was uneventful. On examination, the Hi-Lo Jet^R tube would kink at a point immediately above the cuff when bent slightly.

Discussion

ESWL is a noninvasive procedure to disintegrate urinary tract calculi. Both general and regional anesthesia techniques have been used during ESWL.

Received from the Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, Montefiore Hospital, Pittsburgh, Pennsylvania. Accepted for publication November 1988.

Address correspondence to Dr. Wilks, Department of Anesthesiology, Montefiore Hospital, 3459 Fifth Avenue, Pittsburgh, PA 15213.

©1989 by the International Anesthesia Research Society

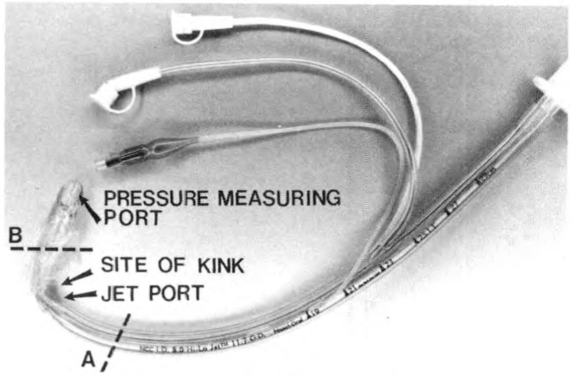


Figure 1. Site of kink is shown. A and B indicate cross sections in Figure 2.

Some studies prefer general anesthesia to control respiration and so minimize renal movement that may displace the calculi (2). When using general anesthesia, HFJV has been advocated to reduce tidal volumes therefore further reducing movement of calculi (2–4).

We have observed a tendency for patients to slump forward during placement into the water bath, causing flexion of the neck. Endotracheal tubes are especially prone to kink when the patient's neck is flexed because the curvature of the endotracheal tube is increased. "Relaxation and forward flexion of the neck and secondary airway obstruction" during lithotripsy was noted by London et al. in awake, sedated patients (2). Repositioning the headrest of the gantry seat did not completely relieve the obstruction of the endotracheal tube in our patient.

Characteristics of endotracheal tubes that are factors in their tendency to collapse or kink include thickness of the tube wall, accessory lumina in the tube wall, ridges in the wall of the tube, and the hardness of the material from which the tube is constructed (5). The Hi-Lo Jet^R tube would be expected to resist kinking because of its relatively thick wall and additional lumina molded within the wall for cuff inflation, jet ventilation and pressure monitoring. However, the Hi-Lo Jet^R tube is not uniformly stiff: at the point where our tube kinked (proximal to the cuff yet distal to the jet port), it is more pliable (Fig. 1 and 2). At this point, the plastic is removed anteriorly on the inside surface of the tube to create an opening for the jet gas delivery port.

The Acutronic 1000^R jet ventilator is equipped with two separate airway pressure sensing systems. The first system senses the patient's airway pressure via the gas delivery tubing during expiration. If the patient's end-expiratory pressure increases above a preset limit, an automatic shut-off will stop ventilation. The second system senses the airway pressure via an auxiliary pressure lumen such as the pressure port of the Hi-Lo Jet^R tube. The distal opening of the lumen of this port lies at the extreme tip of the endotracheal tube. If a high peak inspiratory pressure is detected, the ventilator will automatically stop. The second system also senses the difference between the peak inspiratory pressure and the end expiratory pressure as measured via the pressure-sensing lumen of the Hi-Lo Jet^R tube. If this difference decreases by 50% between respiratory cycles, the ventilator will automatically alarm "patient disconnected" but will not automatically stop ventilation (6).

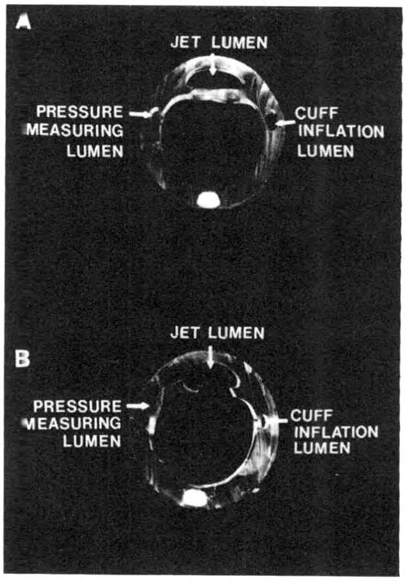


Figure 2. **A**, Cross-section above site of kink. Intact jet lumen is illustrated. **B**, Cross-section below site of kink. The inner wall of the jet lumen has been removed in the manufacturing process. The jet port is located where the plastic is initially absent, but the structural deformity continues along the tube.

In a laboratory setting, we connected the Hi-Lo Jet^R tube to the jet ventilator. As we bent the tube, it kinked as described. The jet port was still patent, and because the actual obstruction was distal to this point, the airflow was directed out the main lumen of the tube to the scavenger system. The ventilator did not trigger an automatic shut-off because neither high end-expiratory nor high inspiratory pressure was generated.

In conclusion, we describe a type of obstruction in a Hi-Lo Jet^R endotracheal tube not previously reported. We believe that the lack of structural uniformity in this type of tube, due to the presence of additional lumina, leads to a tendency for kinking at the specific location described. This case illustrates the importance of connecting the pressure-measuring port of the Hi-Lo Jet^R tube to the Acutronic 1000^R ventilator. If this port had been connected during our case, we would have had a disconnection warning even though our patient was not actually disconnected from the system. Perhaps this alarm should be labeled more descriptively to reflect its broader use. When this ventilator is used with devices other than a Hi-Lo Jet^R tube, there may be no pressure-monitoring lumen available, and, therefore, the anesthesiologist must be aware of the limitations of the built-in alarm systems. We must not extend our confidence in alarms and automatic sensing systems beyond the manufacturer's designs. We must continue to clinically assess our patients.

References

1. Blanc VF, Tremblay NAG. The complications of tracheal intubation: a new classification with a review of the literature. Anesth Analg 1973;53:202–13.
2. London RA, Kudlak T, Riehle RA. Immersion anesthesia for extracorporeal shock wave lithotripsy. Urology 1986;28:86–94.
3. Carlson CA, Gravenstein JS, Banner MJ, Boysen PG. Monitoring techniques during anesthesia and HFJV for extracorporeal shock-wave lithotripsy (abst.). Anesthesiology 1985;63:178A.
4. Berger JJ, Boysen PG, Gravenstein JS, Banner MJ, Carlson CA. Failure of high frequency jet ventilation to ventilate patients adequately during extracorporeal shock-wave lithotripsy. Anesth Analg 1987;66:262–3.
5. Bernhard WN, Yost L, Turndorf H, Danziger F. Cuffed tracheal tubes–physical and behavioral characteristics. Anesth Analg 1982;61:36–41.
6. Operating Instructions, Universal Jet Ventilator-Model AMS 1000, Acutronic Medical Systems AG.

Fifty-Two Years Ago in Anesthesia & Analgesia

E. A. Rovenstine: Anesthesia: organization for teaching. Current Researches in Anesthesia and Analgesia: 1937;16:318–22.

This article gives nice insight into the stature of Rovenstine in the mid-1930s as well as both the state of anesthesia organizations and the stature of anesthesia itself. Rovenstine, when he gave the address represented by this paper, was Professor of Anesthesia at New York University College of Medicine and Director of Anesthesia at Bellevue Hospital in New York City. Both eminent positions with high visibility. The anesthesia organizations in this era are reflected by the fact that, as president of the American Society of Regional Anesthesia, Rovenstine was giving this talk in Atlantic City during American Medical Association Week on the occasion of the Silver Jubilee meeting of the Associated Anesthetists of the United States and Canada held in joint session with the American Society of Anesthetists (sic), the Eastern Society of Anesthetists, the American Society of Regional Anesthesia, and the American Society for the Advancement of General Anesthesia in Dentistry.

The subject of Rovenstine's presentation, education in anesthesia, would today raise no eyebrows. We now take education in anesthesiology as a given. This was by no means the case in 1937. Why? Because prior to 1935, or so, who was there to teach? So few physicians were in anesthesia or entering anesthesia little thought was given to the necessity of formalized teaching of physicians in anesthesia. The infrequent or even rare physician who did specialize in anesthesia either taught himself or got on-the-job training as an apprentice. Clinical coverage preoccupied most physician anesthetists. Research was for few only, and even in the few, research came in as a distant second. Teaching was an even more distant third. Indicative of this state of affairs is the fine point made by Rovenstine in his introduction: prior to 1935 or so, "Over-emphasis of the operative procedure and attention to little more than immediate results protected from criticism anesthesia that offered pain relief, muscle relaxation and returned almost all patients to bed alive."

Surgery was, as Rovenstine emphasizes, about to emerge into a new era in the late 1930s, an era that involved more than technique and pathology, an era in which Anesthesia would become important. As such, the quality and quantity of teaching in anesthesia became important. This required creation of structured educational courses in anesthesia. Education, Rovenstine said, must include teaching medical students about anesthetic techniques as well as applied pharmacology and physiology as they relate to the perioperative period. As a corollary, anesthesia departments in hospitals associated with medical schools must be organized in such a way that university faculty in anesthesia have freedom of time as well as financial support adequate to allow them to reach in the operating room, in the classroom and in the lecture hall. Heady ideas indeed in the 1930s, so heady that it took some teaching hospitals and their universities 40 years to accept them. Noteworthy also is Rovenstine's plea that teaching in anesthesia must entail instruction in all, not just some, anesthetic techniques, plus management of chronic pain problems, inhalation therapy, and clinical research. How revolutionary could one get 52 years ago? And how prescient Rovenstine was. Anesthesiology today consists of what Rovenstine said it should consist of. It took a long time to get there to here.

ANESTH ANALG
1989;69:119–21

Malignant Hyperthermia in a Hemodialysis Patient

Tokuya Harioka, MD, Tetsuhiro Sone, MD, Hiroshi Toda, MD, and Chiyomi Miyake, MD

Key Words: HYPERTHERMIA—malignant.
KIDNEY, FAILURE—malignant hyperthermia.

Malignant hyperthermia (MH) causes severe metabolic disturbances (1). A properly functioning transplanted kidney has been reported to have played a lifesaving role in a case in which MH developed in a renal transplant recipient (2,3). However, hemodialysis patients without kidneys do not have renal compensatory mechanisms to handle the hyperkalemia and metabolic acidosis associated with MH. This study is the first reported case of MH in an anephric long-term hemodialysis patient. We administered calcium and performed urgently needed hemodialysis in the operating room to treat persistent hyperkalemia.

Case Report

A 45-year-old woman weighing 42.8 kg, who had been undergoing hemodialysis three times a week for 7 years, was scheduled for a simple mastectomy. She had undergone no surgery previously except for an arteriovenous shunt under local anesthesia 3 years before. Hemodialysis was performed the day before surgery. Her serum potassium level was 2.9 mmol/L after hemodialysis.

She was given no premedication and was visibly nervous when she arrived at the operating room. Blood gas analysis revealed metabolic acidosis and hyperkalemia despite the hemodialysis on the previous day (Table 1). Anesthesia was induced with 50 mg thiopental and was maintained with 0.8% halothane and 50% oxygen in nitrous oxide during the operation. During induction, multifocal ventricular extra-systoles appeared, but they disappeared when 40 mg lidocaine IV was administered. The masseter muscle was somewhat rigid, but the trachea was intubated without use of a muscle relaxant.

Ninety minutes after induction, blood gas analysis indicated increasing metabolic acidosis and the negative base excess (BE) had reached −13 mmol/L (Figure 1). During the next 40 min the rectal temperature increased from 37.4°C to 38.6°C, and the heart rate increased from 90 to 120 beats/min. The esophageal temperature was taken to confirm hyperthermia; it increased from 38.8°C to 39.6°C in 7 min. With the suspicion of MH, halothane administration was stopped, but the nitrous oxide was continued because of the absence of hypoxemia in the arterial blood sample as shown in Table 1. The patient was vigorously cooled with cold IV solutions, cooling blankets, and ice pads on the body, and 60 mg of dantrolene was given IV. The heart rate and esophageal temperature started to decrease within a few minutes, and the surgery was completed.

In the following hour, the esophageal temperature decreased to 37.5°C, and the BE of arterial blood improved. However, the serum potassium continued to increase to a level of 7.2 mmol/L, and the T waves became "tented" on the electrocardiogram (ECG). We administered 20 mL of 8.5% calcium gluconate IV to treat the hyperkalemia. This promptly corrected the "tented" T waves. Next, hemodialysis was immediately initiated in the operating room because persistent hyperkalemia has been reported during MH in renal transplant recipients (2,3). After 3 hr of dialysis, the serum potassium level decreased to 4.1 mmol/L,

Table 1. Blood Gas Tensions and Serum Potassium (K^+)

	Time After Induction (min)					
	0	90	130	160	190	400
F_IO_2	0.2	0.5	0.5	0.5	0.5	NA
pH	7.38	7.18	7.23	7.53	7.37	7.34
PaO_2 (kPa)*	11.8	23.8	30.1	35.4	36.3	19.2
$PaCO_2$ (kPa)	3.9	5.5	5.3	3.1	4.7	4.8
Base excess (mmol/L)	−6	−13	−10	−3	−5	−5
K^+ (mmol/L)	6.1	6.1	5.8	7.0	7.2	4.1

*kPa × 7.502 = mm Hg. NA = not available. Oxygen was administered through nasal cannulae at a rate of 3l/min.

Received from the Department of Anesthesia, Shimada Municipal Hospital, Shimada, Shizuoka, Japan. Accepted for publication January 16, 1989.

Address correspondence to Dr. Harioka, Department of Anesthesia, Shimada Municipal Hospital, Noda 1200-5, Shimada, Shizuoka 427, Japan.

©1989 by the International Anesthesia Research Society

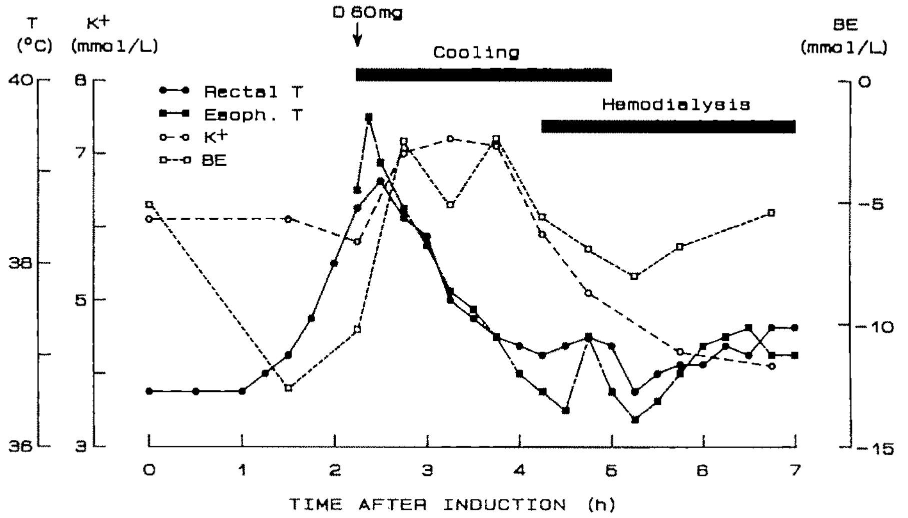


Figure 1. Rectal and esophageal temperatures and serum potassium and base excess (BE) levels. T = temperature; Esoph. = esophageal; K^+ = potassium; BE = base excess; D = dantrolene.

metabolic acidosis was almost corrected, and the temperatures stabilized around 37°C. The patient was sent to the intensive care unit where dantrolene was infused at a rate of 5 mg/hr for 12 hrs to achieve the recommended dose of 2.4 mg/kg of body weight (4).

On the first postoperative day, a slight increase in temperature (37.5°C) persisted, the serum potassium level again increased to 5–6 mmol/L, and the myoglobin level peaked at 132,000 ng/ml (the normal upper limit is 70). Serum creatine kinase levels reached a peak value of 3596 IU/L (the normal upper limit is 80) on postoperative day 2. The remainder of the postoperative course was uneventful.

A month later, a muscle biopsy specimen was removed under local anesthesia and studied for MH susceptibility employing the skinned muscle fiber test (5). The sensitivity of Ca-induced Ca release of the muscle was shown to be significantly higher than that in normal muscle at a Ca ion concentration of 10^{-5} M but not higher at lower Ca ion concentrations.

Discussion

Anesthesia-induced rhabdomyolysis without pyrexia has not been reported except when succinylcholine was used (6–8), and halothane alone does not cause an increase in serum myoglobin (9). Therefore, the simultaneous development of hyperthermia with rhabdomyolysis and myoglobinemia associated with the administration of halothane strongly suggests the development of MH. Rapidly increased metabolic acidosis and the immediate effects of dantrolene support this diagnosis in the present case. The results of the skinned muscle fiber test did not confirm MH susceptibility of the patient, but this is not incompatible with the clinical diagnosis of MH because the test has not yet established a reputation or criteria for susceptibility of MH (10).

There are some unique problems that accompany rhabdomyolysis and/or MH in a hemodialysis patient; the first is the lack of renal regulation of metabolic disturbances, especially the hyperkalemia. The second is the absence of information about the pharmacokinetics of dantrolene in patients either anephric or with chronic renal failure. Hyperkalemia is a life threatening situation during a crisis such as MH even in patients with normal kidneys (1). It can be even more so in anephric patients. Although administration of calcium is the most rapid means to counteract the cardiac effects of potassium (11), the IV administration of calcium during an MH attack is considered dangerous (1,12). However, an increase in serum calcium levels was recently shown not to trigger MH in malignant hyperthermia-susceptible (MHS) pigs (13,14). Moreover, potassium in cardiotoxic concentrations was found to increase the whole body oxygen consumption in MHS pigs (13). In a previous report on MH in a renal transplant recipient, calcium chloride was safely given for the emergency treatment of peaked T wave induced by hyperkalemia (3). Murakawa et al. (15) also used calcium gluconate, safely and effectively, to treat cardiac arrest due to hyperkalemia in a fulminant MH case.

Severe, persistent hyperkalemia during an MH crisis has been reported in kidney transplant recipients despite hemodialysis on the day before surgery (2,3). Disturbances of potassium homeostasis may have contributed to the hyperkalemia. In addition, hyperkalemia developed as the first sign of MH in one case (3). Nevertheless, hyperkalemia before the induction of anesthesia in the present case is puzzling, because the average serum potassium level had been 4.5 ± 0.3 (mean ± SD) mmol/L and had never been above 5.2 mmol/L in the 6 months prior to the surgery, even 2 days after hemodialysis. Cell membrane permeability may have been abnormal before the triggering of MH with halothane. Stress and apprehension are also thought to predispose patients to MH (16), and they may play some role in the present case, too.

Factors influencing dializability of drugs include 1) molecular weight, 2) water solubility, 3) protein binding, and 4) plasma clearance (17). The molecular weight of dantrolene, 399, is relatively small, but its low solubility in water led us to assume it would not be removed by hemodialysis. To prevent a recurrence of MH, we therefore infused dantrolene intravenously at a rate of 5 mg/hr for 12 hrs. The serum concentration of dantrolene could not be measured, but in any event the dose of dantrolene we used prevented a relapse of MH.

In summary, MH developed during breast surgery in a long-term hemodialysis patient as attested to by the abrupt onset of rhabdomyolysis, hyperthermia, hyperkalemia, and metabolic acidosis. The hyperthermia was rapidly reversed with dantrolene and cooling, and the hyperkalemia was treated by urgent hemodialysis in the operating room.

We are grateful to Professor K. Mori, Department of Anesthesiology, Kyoto University for useful suggestions, and Professor M. Endo, Department of Pharmacology, Tokyo University for performing the skinned muscle fiber contraction test.

References

1. Britt BA. Malignant hyperthermia. Can Anaesth Soc J 1985; 32:666–77.
2. Byers DJ, Merin RG. Malignant hyperthermia in a renal transplant recipient. Anesthesiology 1987;67:979–81.
3. Simons ML, Goldman E. Atypical malignant hyperthermia with persistent hyperkalemia during renal transplantation. Can Anaesth Soc J 1988;35:409–12.
4. Flewellen EH, Nelson TE, Jones WP, Arens JF, Wagner GL. Dantrolene dose response in awake man: implications for management of malignant hyperthermia. Anesthesiology 1983;59:275–80.
5. Endo M, Yagi S, Ishizuka T, Horiuti K, Koga Y, Amaha K. Changes in the Ca-induced Ca release mechanism in the sarcoplasmic reticulum of the muscle from a patient with malignant hyperthermia. Biomed Res 1983;4:83–92.
6. Pellicci PM, Paget S, Tsairis P. Post-anesthetic myoglobinuria with acute renal failure (normothermic malignant hyperthermia): a case report. J Bone Joint Surg [Am] 1983;65:413–4.
7. McKishnie JD, Muir JM, Girvan DP. Anesthesia induced rhabdomyolysis—a case report. Can Anaesth Soc J 1983; 30:295–8.
8. Wang JM, Stanley TH. Duchenne muscular dystrophy and malignant hyperthermia—two case reports. Can Anaesth Soc J 1986;33:492–7.
9. Blanc VF, Vaillancourt G, Brisson G. Succinylcholine, fasciculations and myoglobinemia. Can Anaesth Soc J 1986;33:178–84.
10. Øding H. Diagnosis of susceptibility to malignant hyperthermia in man. Br J Anaesth 1988;60:287–302.
11. Black RM. Disorders of serum sodium and serum potassium. In: Rippe JM, Irwin RS, Alpert JS, Dalen JE, eds. Intensive Care Medicine. Boston: Little, Brown, 1985:610–24.
12. Gronert GA. Malignant hyperthermia. Anesthesiology 1980; 53:395–423.
13. Gronert GA, Ahern CP, Milde JH, White RD. Effect of CO_2, calcium, digoxin, and potassium on cardiac and skeletal muscle metabolism in malignant hyperthermia susceptible swine. Anesthesiology 1986;64:24–8.
14. Harrison GG, Morrell DF, Brain V, Jaros GG. Acute calcium homeostasis in MHS swine. Can Anaesth Soc J 1987;34:377–9.
15. Murakawa M, Hatano Y, Magaribuchi T, Mori K. Should calcium administration be avoided in treatment of hyperkalemia in malignant hyperthermia? Anesth Analg 1988;67:604–5.
16. Mogensen JV, Misfeldt BB, Hanel HK. Preoperative excitement and malignant hyperthermia. Lancet 1974;1:461.
17. Gibson TP. Principles of drug dose adjustment during hemodialysis. Am J Kidney Dis 1983;3:111–3.

Intrathecal Narcotics for Labor Revisited: The Combination of Fentanyl and Morphine Intrathecally Provides Rapid Onset of Profound, Prolonged Analgesia

Barbara L. Leighton, MD, Cheryl A. DeSimone, MD, Mark C. Norris, MD,
and Bruce Ben-David, MD*

Key Words: ANESTHESIA, obstetric. ANESTHETIC TECHNIQUES, SPINAL—morphine, fentanyl. ANALGESICS—morphine, fentanyl.

Many anesthesiologists are frustrated by the limitations of currently available techniques for labor analgesia (1). Parenteral medications, commonly used for labor analgesia, can depress both mother and baby without providing adequate pain relief (1,2). Lumbar epidural analgesia, although very effective at relieving the pain of labor, is actually received by only 16% of laboring patients in the United States (1). Reasons cited for the underutilization of this technique include the amount of time required and the poor reimbursement offered (1). Intrathecal morphine (1–2 mg) can be rapidly administered and provides good analgesia for the first stage of labor; however, the associated long latency, high incidence of side effects, and lack of perineal anesthesia severely limit its usefulness (3–6). We hypothesized that the intrathecal administration of a combination of fentanyl, a narcotic with a short latency and a brief duration of action, and a lower dose of morphine might provide satisfactory labor analgesia with a shorter latency and a lower incidence of side effects. Here, we report the results of administering intrathecal fentanyl 25 μg and morphine 0.25 mg to 15 laboring patients.

Methods

After obtaining approval from our institutional review board, we studied 15 healthy parturients, not addicted to opiates, who consented to participate in this study. All women carried healthy, single, term gestations with normal fetal heart rate tracings. We started a slow intravenous infusion of crystalloid solution but did not administer a pre-anesthetic fluid load. An anesthesia resident performed dural puncture with a 25-gauge spinal needle and injected fentanyl 25 μg and morphine 0.25 mg in 2 mL normal saline solution into the cerebrospinal fluid. An observer recorded the time from opening the spinal anesthesia kit to removing the spinal needle from the patient's back. We monitored the fetal heart rate and uterine contractions continuously for 30 min after narcotic administration. We then permitted each patient to ambulate with intermittent fetal heart rate monitoring as allowed by the patient's obstetrician.

Patients rated their pain on a 0–100 scale (0 = no pain, 100 = worst imaginable pain) before intrathecal injection of the narcotics and 5, 15, 20, and 60 min thereafter, and then hourly until delivery. A nurse recorded maternal blood pressure, heart rate, and respiratory rate every 15 min during labor and delivery and then every 60 min until 24 hr after intrathecal narcotic administration. We also monitored the patients' oxygen saturation with a pulse oximeter from the time of delivery of the baby until 12 hr after intrathecal narcotic administration.

If the patient requested further analgesia, we initiated lumbar epidural anesthesia with 12 mL of 0.25% bupivacaine and recorded the duration of pain relief produced by the first epidural bupivacaine injection (the time from bupivacaine injection until either delivery or the patient's next request for analgesia). We did not record further pain scores after injection of the epidural bupivacaine. When the cervix was fully dilated and the fetal head had descended at least 2 cm below the ischial spines, the patient was given either pudendal block anesthesia or injection of local anesthetic epidurally.

Twenty-four hours after intrathecal narcotic administration, we assessed patient satisfaction by asking: "Were you satisfied with the pain relief you

---

Received from the Department of Anesthesiology, Thomas Jefferson University, Philadelphia, Pennsylvania and *Minneapolis Anesthesia Associates, Minneapolis, Minnesota. Accepted for publication January 12, 1989.

Address correspondence to Dr. Leighton, Department of Anesthesiology, 524 Main, Thomas Jefferson University, 111 South 11th Street, Philadelphia, PA 19107.

©1989 by the International Anesthesia Research Society

Table 1. Patient Demographic Data (mean ± SD)

Age (yrs)	27 ± 6
Height (cm)	168 ± 5
Weight (kg)	85 ± 14
Gestational age (wks)	40.3 ± 1.7
Cervical dilation before intrathecal narcotics (cm)	4.9 ± 1.2
No. nulliparous patients	10
First stage labor duration (min)*	207 ± 156
Second stage labor duration (min)†‡	95 ± 56
No. multiparous patients	5
First stage labor duration (min)*	135 ± 109
Second stage labor duration (min)†	41 ± 40
Infant weight (g)	3548 ± 626

*First stage labor duration = time from 4 to 10 cm cervical dilation; †second stage labor duration = time from 10 cm cervical dilation to delivery; ‡excludes the patient who delivered by cesarean section for cephalopelvic dysproportion.

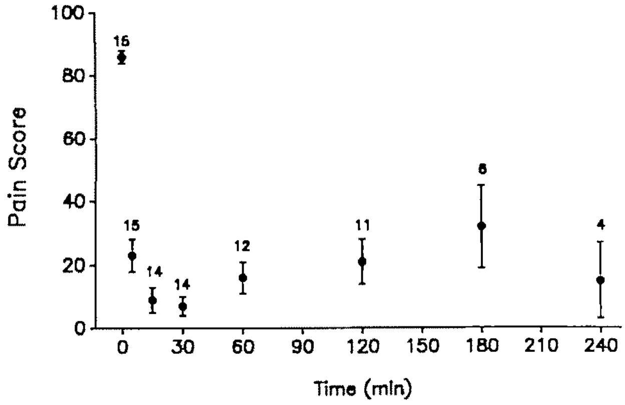


Figure 1. Mean ± SEM pain scores (0 = no pain, 100 = worst imaginable pain) after intrathecal injection of fentanyl 25 μg and morphine 0.25 mg for pain relief during labor. The number of patients still laboring under intrathecal narcotic analgesia appears above each value.

received from the intrathecal narcotics?" and "Would you prefer to receive intrathecal narcotics or an epidural anesthetic during a future labor?" Pain scores are expressed as mean ± SEM, other values as mean ± SD.

Results

Maternal demographic characteristics are described in Table 1. Fourteen patients delivered vaginally (13 spontaneous vaginal deliveries, 1 vacuum extraction); one patient delivered a 4,640-g infant by cesarean section for cephalopelvic disproportion.

Intrathecal injection of the narcotic solution took 13 ± 4 min. All patients had significant pain relief within 5 min of the narcotic injection (Figure 1). Table 2 shows the duration of intrathecal narcotic analgesia.

Table 2. Duration of Analgesia During Labor After Intrathecal Injection of a Combination of Fentanyl and Morphine

	Oxytocin Induction	Spontaneous Labor
Comfortable until delivery*	222 ± 196 (N=3)	187 ± 148 (N = 6)
Epidural anesthesia later required*	139 ± 57 (N= 5)	145 (N = 1)
Duration of analgesia after first epidural bupivacaine dose†	170 ± 91	110

*Analgesic duration expressed as minutes (mean ± SD) from administration of intrathecal narcotics until delivery or institution of epidural anesthesia; †duration of analgesia expressed as minutes (mean ± SD) from injection of epidural bupivacaine until the patient's next request for analgesia.

Nine patients did not need epidural injection of bupivacaine and delivered vaginally with supplemental pudendal block anesthesia. Six patients had lumbar epidural analgesia induced 140 ± 51 min after intrathecal narcotic administration; five of these patients delivered vaginally under epidural analgesia and one patient delivered by cesarean section.

We found no clinically significant changes in maternal vital signs after intrathecal narcotic administration. Respiratory rates were ≥16 for the first 24 hr in all patients. Arterial oxygen saturation below 90% did not occur. Four patients received nalbuphine 5–10 mg IV during labor to treat itching or nausea. After the first four patients in this series reported new or more severe itching and vomiting after delivery, we gave the remaining patients prophylactic postpartum narcotic antagonists. Moderate to severe postpartum itching and vomiting occurred in seven of the eight patients given either no prophylactic narcotic antagonists (N = 4) or oral naltrexone 12.5 mg (N = 4). Three of the five patients given a continuous infusion of naloxone 0.2 mg/hr had mild postpartum itching (N = 2) or nausea (N = 1). The two patients given naltrexone 25 mg had no postpartum side effects. One patient had a mild positional headache that started 2 days postpartum and resolved without treatment.

The patients' obstetricians noted no clinically significant changes in the fetal heart rate patterns during the 30-min period after intrathecal narcotic administration. Two infants had 1-min Apgar scores of 6; all other 1-min and all 5-min Apgar scores were ≥7.

All 10 of the nulliparous patients in this series said that they were satisfied with their analgesia and would like to receive intrathecal narcotic analgesia during a future labor. The five multiparous patients in this series had all had lumbar epidural analgesia during a previous labor. Two of these multiparous patients said they preferred intrathecal narcotic analgesia, whereas three preferred epidural analgesia. The three multiparous patients who said they preferred epidural analgesia delivered 29 ± 20 min after narcotic administration, received naltrexone 12.5 mg (N = 2) or no narcotic antagonists (N = 1) after delivery, and had severe postpartum itching.

Discussion

One of the authors (BBD) began to use intrathecal narcotic analgesia to provide effective yet inexpensive analgesia for laboring women who subscribed to a health maintenance organization which was unwilling to pay for epidural analgesia. We subsequently tried this technique at Thomas Jefferson University Hospital and found that a number of our patients and obstetricians prefer intrathecal narcotic to epidural analgesia.

Laboring patients want rapid onset of pain relief. Analgesic latency is 10–20 min with epidural bupivacaine anesthesia (7) and 15–60 min with intrathecal morphine analgesia (3–6). In contrast, we achieved profound analgesia within 5 min after the intrathecal injection of a combination of fentanyl and morphine. Our results are consistent with data from animal studies in which intrathecal fentanyl provides analgesia with an onset of less than 3 min and a duration of about 60 min (8).

An ideal analgesic for labor should have a long duration of action and provide consistent pain relief, minimizing both the physician time needed for maintenance and undesirable side effects (9). With bupivacaine, intermittent epidural injections for relief of pain during labor requires that injections be repeated every 92 ± 5 min (10), whereas continuous epidural infusions need to be checked hourly (11). Intrathecal morphine 1–2 mg provides profound analgesia starting about 60 min after injection and lasting until the perineum is distended by the fetus; however, bothersome intrapartum maternal side effects occur in 72%–100% of the patients (3–6). The doses of intrathecal fentanyl and morphine that we used provided pain relief starting within 5 min after injection and lasting until perineal distension in 60% of the patients and 140 ± 51 min of analgesia in the remaining patients. Intrapartum side effects, which were easily treated with nalbuphine, occurred in only 27% of the patients. Intrathecal narcotics may even potentiate the effects of subsequent epidural bupivacaine, because the duration of effective analgesia from the first epidural injection of bupivacaine in this series (170 ± 91 min) was longer than that reported for similar doses of epidural bupivacaine without prior injection of intrathecal narcotics (92 ± 5 min) (10).

Ideally, analgesia for labor should relieve pain while maintaining maternal expulsive forces of labor and motor tone (9). Lumbar epidural analgesia frequently fails to meet this criterion, because up to half of the women receiving lumbar epidural analgesia have at least partial motor block at the time of delivery (12). Intrathecal narcotics, however, act on spinal opiate receptors without affecting motor neurons so that the patient's motor function is unimpaired (8).

Patient satisfaction with intrathecal narcotic analgesia in this series (80%) is comparable with previously reported maternal satisfaction with epidural analgesia (79%) (13). We have been particularly satisfied with intrathecal narcotic analgesia in patients who had wanted natural childbirth but became overwhelmed by the pain of labor, in patients in latent labor who have had poor pain relief with parenteral narcotics, and in patients in active labor who want to remain ambulatory but want pain relief. In addition, intrathecal narcotics may be preferable to epidural anesthesia for patients who need a high systemic vascular resistance to maintain hemodynamic stability, such as patients with Eisenmenger's syndrome, valvular heart disease, or hypovolemia. Since the completion of this study, we have administered intrathecal narcotics to one patient with valvular heart disease and one patient with recent blood loss from a partial placental abruption. Maternal vital signs and fetal heart rate patterns did not change in either patient, and both had uneventful vaginal deliveries of healthy babies without needing further anesthesia.

One drawback of intrathecal narcotic labor analgesia is the lack of perineal anesthesia for operative delivery. The nine patients in this series who did not require an epidural during the first stage of labor did not report increased pain during the descent of the fetal head. All nine obtained good analgesia for their episiotomies with pudendal nerve blocks.

Pruritus and vomiting can cause discomfort for the parturient given intrathecal narcotics. The incidence of pruritus and vomiting after intrathecal narcotic administration varies among different patient populations, with patients experiencing the least pain generally having the highest incidence of side effects (14). Our results corroborate this finding; pruritus and vomiting were more common and severe after delivery of the baby. We, therefore, started administering prophylactic narcotic antagonists 30 min after delivery. Appropriate doses of either naloxone or naltrexone should effectively prevent side effects; however, the use of naltrexone, an oral long-acting narcotic antagonist, avoids the time and expense involved in maintaining a naloxone infusion (15). Our current practice is to administer naltrexone 25 mg orally 30 min postpartum to all patients who deliver vaginally within 12 hrs of receiving intrathecal narcotics for labor.

We now routinely offer both intrathecal narcotic and epidural analgesia to our laboring patients, and intrathecal narcotics now constitute about 8% of the labor anesthetics we administer. Opinions about intrathecal narcotics among our obstetrical colleagues range from one obstetrician who has suggested renaming the technique "paradise anesthesia" and recommends it to all his patients, to others who prefer epidural anesthesia to achieve complete perineal anesthesia for delivery. We believe that this simple technique is advantageous in many clinical circumstances and warrants further controlled studies.

References

1. Gibbs CP, Krischer J, Peckham BM, Sharp H, Kirschbaum TH. Obstetric anesthesia: a national survey. Anesthesiology 1986; 65:298–306.
2. Levinson G, Shnider SM. Systemic medication for labor and delivery. In: Shnider SM, Levinson G, eds. Anesthesia for Obstetrics. 2nd ed. Baltimore: Williams & Wilkins. 1987: 89–108.
3. Baraka A, Noueihid R, Hajj S. Intrathecal injection of morphine for obstetric analgesia. Anesthesiology 1981;54:136–40.
4. Scott PV, Bowen FE, Cartwright P, et al. Intrathecal morphine as sole analgesic during labor. Br Med J 1980;281:351–3.
5. Bonnardot JP, Maillet M, Cplau JC, Millot F, Deligne P. Maternal and fetal concentration of morphine after intrathecal administration during labour. Br J Anaesth 1982;54:487–9.
6. Hee P, Sorensen SS, Bock JE, Fernandes A, Steentoft A. Intrathecal administration of morphine for the relief of pains in labour and estimation of maternal and fetal plasma concentration of morphine. Eur J Obstet Gynecol Reprod Biol 1987; 25:195–201.
7. Albright GA. Lumbar epidural anesthesia. In: Albright GA, Ferguson JE, Joyce TH, Stevenson DK, eds. Anesthesia in Obstetrics: Maternal, Fetal, and Neonatal Aspects. Boston: Butterworths, 1986:278–309.
8. Yaksh TL, Rudy TA. Studies on the direct spinal action of narcotics in the production of analgesia in the rat. J Pharmacol Exp Ther 1977;202:411–28.
9. Bromage PR. Choice of local anesthetics in obstetrics. Part 1: General considerations. In: Shnider SM, Levinson G, eds. Anesthesia for Obstetrics, 2nd ed. Baltimore: Williams & Wilkins, 1987:59–68.
10. Eisenach JC, Grice SC, Dewan DM. Epinephrine enhances analgesia produced by epidural bupivacaine during labor. Anesth Analg 1987;66:447–51.
11. Shnider SM, Levinson G, Ralston DH. Regional anesthesia for labor and delivery. In: Shnider SM, Levinson G, eds. Anesthesia for Obstetrics, 2nd ed. Baltimore: Williams & Wilkins, 1987:109–22.
12. Chestnut DH, Vandewalker GE, Owen CL, Bates JN, Choi WW. The influence of continuous epidural bupivacaine analgesia on the second stage of labor and method of delivery in nulliparous women. Anesthesiology 1987;66:774–80.
13. Crawford JS. The second thousand epidural blocks in an obstetric hospital practice. Br J Anaesth 1972;44:1277–87.
14. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.
15. Mok MS, Shuai SP, Lee C, Lee TY, Lippmann M. Naltrexone pretreatment attenuates side effects of epidural morphine. Anesthesiology 1986;65:A200.

Two Cardiac Arrests after Needle Punctures in a Patient with Mitral Valve Prolapse: Psychogenic?

Zef A. Abraham, MD, and David Eric Lees, MD

Key Words: HEART, ASYSTOLE—mitral valve prolapse.

Emotional stress is known to alter the balance of the autonomic nervous system. Painful stimuli imposed on an already anxious individual may exacerbate autonomic responses. A case is described in which a young woman with a history of mitral valve prolapse (MVP) suffered two episodes of cardiac arrest after needle punctures.

Report Of A Case

A 70-kg, 160-cm, 33-yr-old woman presented to the pain service in our ambulatory surgery unit for diagnostic epidural block to determine whether visceral pathology was the cause of her long history of abdominal pain (1), initially attributed by her gynecologist to endometriosis. Her medical history included a 3-month history of occasional chest pain that had been attributed to mild mitral valve prolapse after workup that included echocardiography. In addition, she had mild asthma, her last attack 2 yr previously, but was taking no asthma medications. She had had both spinal and general anesthesia, without incident, for multiple laparoscopies and an abdominal hysterectomy in the past because of her endometriosis. Medications included 400 mg danazol twice a day and 10 mg propranolol as needed for chest pain, which she had taken on the morning of her scheduled procedure. Physical examination revealed an apprehensive young woman with an arterial blood pressure of 120/70 mm Hg and a heart rate of 70 beats/min, without abnormal physical findings aside from well-healed and nontender abdominal scars.

On arrival in our ambulatory unit, she was unpremedicated and mildly anxious; an automated sphygmomanometer and electrocardiograph (ECG) leads were applied, and a 22-gauge peripheral venous catheter was inserted. The patient was placed in the right lateral decubitus position and the lower back aseptically cleansed and draped. No intraoperative sedation was given. With use of a 25-gauge needle and tuberculin syringe, 1 mL 1.5% lidocaine was injected subcutaneously at the L3–L4 interspace. Within approximately 5 sec after needle insertion, the patient suddenly developed a sinus bradycardia of 40 beats/min from an initial rate between 70 and 80 beats/min that rapidly progressed to asystole; ventilation ceased and the patient lost consciousness. She was rapidly placed in the supine position and positive pressure ventilation with oxygen was begun. The heart rate rapidly returned to 70–80 beats/min as did spontaneous ventilation. No resuscitative medications were administered because of the rapidity of recovery. The patient then suddenly developed a grand mal seizure, which also spontaneously resolved in 5–10 sec. The only therapy given was oxygen and airway control by jaw-thrust.

After approximately 5 min of postictal depression during which time the vital signs remained stable, there was a return to her normal level of consciousness. A 12-lead ECG showed normal sinus rhythm at 75 beats/min without ischemic changes. When a 25-gauge needle was inserted to obtain an arterial blood sample, within approximately 5 sec the patient complained of chest pain and dizziness, followed by a second episode of sinus bradycardia to a heart rate of 40 beats/min and then asystole. External cardiac compression was started, 0.4 mg IV atropine was administered, and controlled ventilation with an $F_{I_{O_2}}$ of 1.0 via mask and Ambu bag was instituted. An arterial blood sample had a pH_a of 7.46, Pa_{CO_2} of 29 mm Hg, Pa_{O_2} of 181 mm Hg, HCO_3^- 21 mEq/L, a base excess of −1 mEq/L, and an O_2 saturation of 99%. Heart rate rapidly returned to 90 beats/min, and spontaneous ventilation resumed at 15 breaths/min.

Received from the Department of Anesthesiology, New York Medical College, Valhalla, New York. Accepted for publication February 23, 1989.

Address correspondence to Dr. Abraham, Yale University School of Medicine, Department of Anesthesiology, 333 Cedar Street, New Haven, CT 06510.

©1989 by the International Anesthesia Research Society

At this point, the procedure was cancelled and the patient transferred to the medical intensive care unit (ICU) for monitoring and evaluation.

Subsequent evaluation included: 1) serial ECGs that showed normal sinus rhythm and no ischemic changes; 2) repeatedly normal plasma levels of cardiac isoenzymes; 3) a normal exercise stress test; 4) mild mitral valve prolapse on echocardiography; 5) a single premature atrial contraction and 2 single premature ventricular contractions during 24 hr Holter monitoring; 6) a normal chest x-ray; 7) serum levels of sodium 138 mEq/L, potassium 4.5 mEq/L, chloride 98 mEq/L, CO_2 27 mEq/L, blood urea nitrogen 11 mg/dL, creatinine 0.9 mg/dL, glucose 127 mg/dL, uric acid 3.4 mg/dL, creatine phosphokinase 94 u/L (normal <195), lactate dehydrogenase 161 u/L (normal <273), serum glutamic-oxaloacetic transaminase 16 u/L (normal <37),serum glutamic-pyruvic transaminase 22 u/L, GGT 14 u/L, alkaline phosphatase 45 u/L, total bilirubin 0.3 mg/dL, cholesterol 321 mg/dL (normal <240), total protein 7.8 g/dL, albumin 4.8 g/dL, calcium 9.2 mg/dL, PO_4^- 3.7 mg/dL, globulin 3.0 g/dL, anion gap 13; 8) hemoglobin 16.2 g/dL, hematocrit 46.6%, white cell count 8400 cells/mm^3, and platelet count 53.4 × 10^4 cells/mm^3; and 9) prothrombin time of 11.6/11.2 and a partial thromboplastin time of 21.9/24.2 sec.

The patient was observed in the ICU for 48 hr during which time she remained stable throughout; subsequently she was transferred to a medical ward, where she continued to do well. She was discharged 4 days later.

Discussion

Cardiac arrest in this patient could be attributed to a number of factors acting alone or in concert. These include: 1) mitral valve prolapse; 2) a level of anxiety high enough to set the stage for psychogenic cardiac arrest; 3) the propranolol she had taken; and 4) an adverse reaction to lidocaine.

Mitral valve prolapse has been associated with various cardiac arrhythmias, often asymptomatic and most commonly affecting women in their fourth decade, with a reported 1.4% incidence of sudden death (2). Common MVP symptoms include palpitations, syncope, and chest pain. A number of patients with this condition present with associated psychiatric disorders. Sudden death in patients with MVP has been attributed to the arrhythmogenic effects of autonomic, metabolic, and mechanical factors (3). Exercise stress testing may induce arrhythmias, including premature atrial contractions (PAC), premature ventricular contractions (PVC), supraventricular tachycardia (SVT), ventricular tachycardia (VT), and bradyarrhythmias (4).

Psychologic stress is associated with increased autonomic activity, involving sympathetic or parasympathetic systems. When stress occurs in the "passive" patient who is unable to modify his or her position, the cardiovascular response is predominantly vagally mediated. When, however, the stress occurs in the "active" patient who can modify his or her position, the response is usually mediated by the sympathetic nervous system (5). The patient described in the previous section would fit the passive category. There are many reports of cardiac death in which the arrest has been precipitated or influenced by stressful life experiences. Electron microscopic studies have shown specific myocardial microanatomical changes pertaining to sudden death (6). These changes are known as contraction bands or coagulative myocytolysis and are the only pathological findings in a large proportion of cases of sudden cardiac death. These myocardial changes can be induced in animals by the infusion of catecholamines. MVP often occurs in patients with a variety of anxiety syndromes characterized by hyperdynamic β-adrenergic secretion (7).

Pharmacologically active blood levels of propranolol as a contributing factor in this patient's cardiac arrests are unlikely. Propranolol is known to cause atrioventricular dissociation and cardiac arrest in patients with preexisting partial heart block through its negative chronotropic effect (8). This patient, however, was in all likelihood taking a subtherapeutic dose (10 mg orally as needed for chest pain) and did not have a known preexisting conduction defect.

An adverse lidocaine reaction is also unlikely. Although toxic doses of lidocaine have been associated with sinus bradycardia as well as seizures (9), the dose administered, 15 mg subcutaneously, is well below the toxic dose. A true hypersensitivity reaction is also unlikely because she did not develop symptoms typical of an allergic response (e.g., erythema, bronchospasm). Allergic reactions to local anesthetics usually involve drugs of the ester variety; lidocaine is an amide and true allergy to this class is extremely rare (10). In addition, this patient served as her "own control" in that she developed a second cardiac arrest after a mere arterial puncture, without the administration of any drug.

As mentioned previously, this patient had a 3-month history of chest pain before the attempted diagnostic epidural blockade, which was attributed to MVP as diagnosed by echocardiography. It is unclear to what extent the possibility of coronary artery disease was ruled out at that time. Coexisting coronary artery disease, however, does appear to be excluded by the extensive evaluation this patient underwent after the two cardiac arrests.

The patient had no cardiovascular response to insertion of a needle for peripheral intravenous infusion before the needle sticks for initiation of regional anesthesia and blood gas sampling, which led to her subsequent cardiac arrests. In addition, she had no adverse sequelae to peripheral venipuncture for venous blood sampling in the ICU. This paradox, although difficult to explain, may be attributable to the fact that peripheral venous cannulation was perceived by this patient to be a less painful procedure, and as she had previously had venipunctures without difficulty, she may have been favorably conditioned to this procedure.

In summary, a case is presented in which an anxious patient with a history of MVP, occasionally taking propranolol, suffered two cardiac arrests during an attempted diagnostic lumbar epidural anesthesia. The probable causative factors discussed in this report included MVP and a high level of anxiety acting in concert with the cardiac arrests' being subsequent to both. It is unclear whether psychogenic factors or the MVP were the primary event. The possibility of malignant arrhythmia or cardiac arrest must not be taken lightly in patients with MVP, as a 1.4% incidence of sudden death represents a large patient population on a basis of an estimated 6% prevalence of MVP in the adult population (11). We believe that regional anesthesia in patients with MVP should be undertaken with proper monitoring, IV access, and the immediate availability of resuscitative equipment and medication. Preoperative anticholinergic and sedative administration should also be considered in patients with MVP.

References

1. Cousins MJ, Bridenbaugh PO. Neural Blockade in Clinical Anesthesia and Management of Pain, 2nd ed. Philadelphia: J. P. Lippincott, 1988:887.
2. Swartz MH, Teichholz LE, Donoso E. Mitral valve prolapse. A review of associated arrhythmias. Am J Med 1977;62:377–89.
3. Kligfield P, Levy D, Devereux RB, Savage DD. Arrhythmias and sudden death in mitral valve prolapse. Am Heart J 1987;113:1298–307.
4. Shah VK, Pahalajani DB, Gandhi MJ, Pandey BJ, Punjabi AH. Arrhythmias in mitral valve prolapse. Indian Heart J 1986; 38:404–8.
5. Frerichs RL, Campbell J, Bassell GM. Psychogenic cardiac arrest during extensive sympathetic blockade. Anesthesiology 1988;68:943–4.
6. Siltanen P. Stress, coronary disease, and coronary death. Ann Clin Res 1987;19:96–103.
7. Rosenman RH. The impact of anxiety on the cardiovascular system. Psychosomatics 1985;26(suppl):6–17.
8. Weiner N. Drugs that inhibit adrenergic nerves and block adrenergic receptors. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The Pharmacological Basis of Therapeutics, 7th ed. New York: Macmillan, 1985:198.
9. Covino BG, Vassallo HG. Local Anesthetics: Mechanisms of Action and Clinical Use. New York: Grune & Stratton, 1976: 145.
10. Aldrete JA, Johnson DA. Allergy to local anesthetics. JAMA 1969;207:356–7.
11. Miller RD. Anesthesia, 2nd ed. New York: Churchill Livingstone, 1986:290.

ANESTH ANALG 129
1989;68:129–31

Modification of an Eschmann Introducer to Permit Measurement of End-Tidal Carbon Dioxide

Alan A. Artru, MD, Allison B. Schultz, MD, and Juan J. Bonneu

Key Words: INTUBATION, TRACHEAL. EQUIPMENT, ESCHMANN INTRODUCER.

The Eschmann Introducer for Endotracheal Tube (Downs Surgical, Decatur, Ga) is a hollow, woven, flexible stylet that is 60 cm in length. When conventional endotracheal intubation under direct vision cannot be performed because the glottic opening cannot be visualized, tracheal intubation may be accomplished by placing the Eschmann Introducer into the trachea and advancing the endotracheal tube over the introducer. The Eschmann Introducer can be placed into the trachea by internal palpation of posterior pharyngeal and glottic structures or with the aid of a laryngoscope, by directing the introducer toward the suspected site of the glottis as indicated by the posterior pharyngeal and supraglottic structures that are able to be visualized.

One concern with this method of intubation is the need for a reliable indicator that the introducer is located in the trachea before advancing the endotracheal tube. The customary indicator, the feeling of "resistance" as the distal tip of the introducer encounters the tracheal carina or major bronchi, is subjective and therefore liable to interpretive error. Measurement of end-tidal carbon dioxide is reported to be a reliable method of assuring tracheal placement (1–3). We hypothesized that it should be a simple matter to modify the Eschmann Introducer for end-tidal gas sampling because it is hollow and modifications similar to what would be needed for end-tidal gas sampling were recently described (4,5).

One way to determine whether measurement of end-tidal carbon dioxide is a more reliable indicator of tracheal placement than is the feeling of "resistance" would be to compare incidences of successful tracheal placement with the two techniques in patients requiring tracheal intubation but in whom the glottic opening cannot be visualized. However, it would be unsafe to undertake such a study without first being assured that end-tidal carbon dioxide could be measured at least as often as "resistance" could be felt with the Eschmann Introducer. Accordingly, the present study was designed to determine whether the likelihood of end-tidal carbon dioxide measurement was comparable with that of the feeling of "resistance." For purposes of patient safety, the study included only patients in whom the glottic opening could be visualized. An Eschmann Introducer was modified so that it could be used for gas sampling. End-tidal carbon dioxide was measured and "resistance" was felt both when the introducer was known to have entered the trachea and when it was known to have entered the esophagus.

Methods

The Eschmann Introducer was modified by drilling four holes, 1 mm in diameter, through the wall of the introducer and into the central, hollow lumen (3 mm ID). The holes were placed on the distal portion of the catheter between 2.5 and 4.0 cm from the tip. The proximal tip of the introducer was cut off and a standard 4 mm ID "female" adapter was attached (Figure 1).

The protocol for this study was approved by the Human Subjects Committee of the University of Washington. Informed consent was obtained in 35 patients aged 18 to 65 years of ASA physical status I or II. Patients breathed oxygen through a standard anesthesia circle system and mask for 5 min before induction of anesthesia. Thiopental 3–6 mg/kg was given intravenously to induce anesthesia and pancuronium 0.1–0.15 mg/kg was given intravenously to provide muscle relaxation. Patients were ventilated

---

Received from the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington.

Presented in part at the 1987 Western Anesthesia Residents' Conference, Annual Meetings. San Francisco, California, April 24–26. Accepted for publication February 22, 1989.

Address correspondence to Dr. Artru, Department of Anesthesiology, RN-10, University of Washington School of Medicine, Seattle, WA 98195.

©1989 by the International Anesthesia Research Society

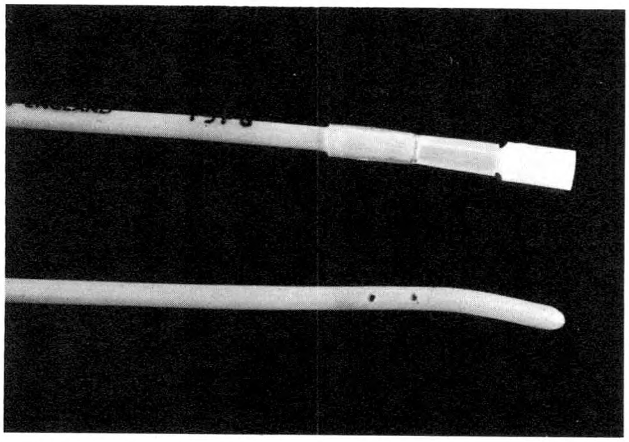


Figure 1. The distal and proximal portions of a modified Eschmann Introducer are shown. The distal portion was modified by drilling four holes, 1 mm in diameter, through the wall of the introducer and into the central, hollow lumen of the introducer. The proximal portion was modified by cutting off the closed tip and attaching a "female" adapter, 4 mm ID, with use of heat-shrink tubing and silicon sealant. A route was thus created for drawing gas from outside the distal portion of the introducer up through the hollow lumen of the introducer and into a gas analyzer.

with isoflurane in oxygen with use of the circle system and mask until the neuromuscular response to nerve stimulation disappeared.

Direct laryngoscopy was then performed. If the vocal cords were not clearly visualized, the patient was excluded from the study. Where the vocal cords were clearly visualized, an endotracheal tube was inserted into the trachea and the endotracheal tube cuff inflated. The modified Eschmann Introducer was passed through the endotracheal tube and advanced until "resistance" was encountered or the distal tip was 40 cm beyond the mouth. We believed that it should not be necessary to pass the introducer more than 40 cm beyond the mouth because in adult patients the usual distance from the mouth to the tracheal carina is 28–32 cm (1). The gas sampling tubing from a mass spectrometer (Perkin-Elmer, Applied Science Division, Pomona, Calif) was attached to the proximal end of the introducer at the adapter. Gases from the distal portion of the introducer were continuously sampled for 30 sec and mean end-tidal carbon dioxide concentration was recorded. Next, the gas-sampling tubing from the mass spectrometer was removed, and the gas-sampling tubing from a Tri-Med system (Biochem International, Inc., Waukesha, Wis) was attached to the proximal end of the introducer. Gases from the distal portion of the introducer again were continuously sampled for 30 sec, and the presence or absence of carbon dioxide was recorded. With the Tri-Med system, if no carbon dioxide was detected after 30 sec, the introducer was pulled back 5 cm and gases were sampled for an additional 30 sec.

Table 1. Incidence of Feeling of "Resistance" and Measurement of End-Tidal Carbon Dioxide After Placement of Eschmann Introducer into the Trachea or Esophagus (N = 35)

	Introducer in Trachea or Bronchus	Introducer in Esophagus or Stomach
"Resistance" felt	35/35	0/35
Carbon dioxide detected by mass spectrometry	35/35	0/35
Carbon dioxide detected by Tri-Med system*	30/35	0/35

*Initial results: carbon dioxide was detected in the remaining 5/5 patients when the introducer was pulled back 5 cm.

Once gas sampling from the trachea was completed, the Eschmann Introducer was removed from the endotracheal tube, the standard circle system was attached to the endotracheal tube, and the patient's lungs were ventilated. Direct laryngoscopy again was performed, the esophagus was visualized, and the modified Eschmann Introducer was passed into the esophagus. Gas sampling was again attempted after the steps outlined in the previous paragraph.

We computed the proportion of cases where "resistance" was felt and where end-tidal carbon dioxide was detected both when the introducer was seen to have entered the trachea and when it was seen to have entered the esophagus. Also computed were mean values ± SD for end-tidal carbon dioxide during 0–0.5 min after intubation (sampled via introducer) and at 1.5–2.0 min after intubation (sampled from the standard circle system).

Results

Thirty-five patients met the inclusion criteria of clearly visualized vocal cords and esophagus under direct laryngoscopy. Mean (±SD) patient characteristics included age 45 ± 13 years, height 165 ± 8 cm and weight 68 ± 10 kg.

When the Eschmann Introducer was seen to have entered the trachea, "resistance" was felt in 35 of 35 patients (Table 1). Similarly, end-tidal carbon dioxide was detected by mass spectrometry in 35 of 35 patients. Mean end-tidal carbon dioxide was 28 ± 6 mm Hg. Carbon dioxide was initially detected in 30 of 35 patients with use of the Tri-Med system. Thirty sec later, after the pulling back of the Eschmann Introducer 5 cm, carbon dioxide was detected in 5 of 5 patients in whom carbon dioxide was not initially detected.

When the Eschmann Introducer was seen to have entered the esophagus, "resistance" was felt in none of 35 patients. Similarly, end-tidal carbon dioxide was detected in none of the 35 patients with either mass spectrometry or the Tri-Med system. At 1.5 min after tracheal intubation, end-tidal carbon dioxide measured by mass spectrometry was 31 ± 4 mm Hg.

Assuming that tracheal placement was the desired goal, there were no false positives or negatives with the feeling of "resistance" (when the introducer was inserted through an endotracheal tube), nor with carbon dioxide measurement by mass spectrometry. With the Tri-Med system, the initial false negative rate was 5/35 and there were no false positive results.

Discussion

The results of this study indicate that when the Eschmann Introducer is known to have entered the trachea, both the feeling of "resistance" or the measurement of end-tidal carbon dioxide by mass spectrometry are reliable indicators that the introducer is in the trachea or bronchus. Measurement of carbon dioxide with the Tri-Med system was not a reliable indicator that the introducer was in the trachea as the false negative rate was 14%. The difference in results between mass spectrometry and the Tri-Med system probably relates to the difference in gas flow characteristics of each system. Both the mass spectrometer used here and the Tri-Med system aspirate gas at about 250 mL/min. However, the maximum negative pressure generated by the mass spectrometer (>110 cm H_2O) is substantially greater than that generated by the Tri-Med system (about 50 cm H_2O). Consequently, the mass spectrometer may overcome partial obstruction of side holes on the introducer by tracheal mucosa, secretions, etc., allowing end-tidal gases to be sampled, whereas the Tri-Med system may not. The present results also indicate that when the Eschmann Introducer is known to have entered the esophagus, both the feeling of no "resistance" or the measurement of no end-tidal carbon dioxide by mass spectrometry are reliable indicators that the introducer is not in the trachea.

It should be emphasized that in this study the feeling of "resistance" and measurement of end-tidal carbon dioxide were assessed only after the Eschmann Introducer was placed in either the trachea or esophagus after endotracheal intubation under direct visualization. In clinical practice, the Eschmann Introducer generally is used to aid intubation only in cases where the vocal cords cannot be directly visualized. Also, situations may occur where either the feeling of "resistance" or measurement of end-tidal carbon dioxide may provide misleading information. For example, it is possible that "resistance" may not be felt when the introducer is in the trachea or bronchus when these structures are abnormal, e.g., tracheomalacia, tracheocele, bronchocele, etc. "Resistance" may be felt when the introducer is not in the trachea, e.g., with tumor impinging on the esophagus or stomach, etc.

Because reasons for failure with feeling "resistance" also would not usually cause failure with measurement of carbon dioxide, the authors recommend that the Eschmann Introducer should be modified to permit gas sampling before it is used as an aid to tracheal intubation. This procedure would permit both "resistance" and carbon dioxide to be used to indicate whether the introducer has been placed into the trachea or bronchus. One benefit of carbon dioxide measurement is that it is a quantitative, documentable measure. A second benefit is that the availability of carbon dioxide measurement may reduce the need for repeated advancing and withdrawing of the introducer that may be necessary to satisfy the operator that "resistance" truly is felt. Repeated advancing and withdrawing of the introducer may traumatize the trachea or bronchus causing edema, bleeding, or perforation.

References

1. Birmingham PK, Cheney FW, Ward RJ. Esophageal intubation: a review of detection techniques. Anesth Analg 1986;65:886–91.
2. Linko K, Palaheimo M, Tammisto T. Capnography for detection of accidental oesophageal intubation. Acta Anaesthesiol Scand 1983;27:199–202.
3. Murray IP, Modell JH. Early detection of endotracheal tube accidents by monitoring carbon dioxide concentration in respiratory gas. Anesthesiology 1983;59:344–6.
4. Bedger RC jr, Change J-L. A jet-stylet endotracheal catheter for difficult airway management. Anesthesiology 1987;66:221–3.
5. Freund PR, Rooke A, Schwid H. Retrograde intubation with a modified Eschmann stylet. Anesth Analg 1987;67:605–6.

Fatal Air Embolism in an Adolescent with Duchenne Muscular Dystrophy during Harrington Instrumentation

Scott A. Lang, MD, Peter G. Duncan, MD, FRCPC, and Pierre R. Dupuis, MD, FRCPS

Key Words: ANESTHESIA, ORTHOPEDIC—air embolism. EMBOLISM—air.

Fatal air embolism can occur during a variety of surgical procedures (1,2). However, it has not been previously associated with the complications of Harrington instrumentation (3,4). We report a fatal outcome from this complication and suggest that other reported untoward outcomes may have been due to a similar pathologic process.

Case Report

A 16-yr-old boy with confirmed Duchenne muscular dystrophy was scheduled to undergo posterior spinal fusion to arrest progressive scoliosis. There was no history of either symptomatic respiratory complications or any condition compatible with left or right ventricular failure. The disease had left him confined to a powered wheelchair, with only minimal function of his upper extremities.

Physical examination revealed a 30-kg boy with marked scoliosis (Cobb's angle, 70°) and muscle wasting who was unable to ambulate. There was a loud P2 suggestive of cor pulmonale, although the scaphoid shape of his chest distorted auscultatory findings. Lung fields were clear bilaterally. The electrocardiogram (ECG) revealed a pattern of right bundle branch block. Pulmonary function tests documented a forced vital capacity (FVC) of 30 $ml \cdot kg^{-1}$ (1.16 L) and a forced expiratory volume (FEV) in 1 sec (FEV_1) of 1.1 L. Results of routine biochemistry and hematologic workup were unremarkable.

Anesthesia was induced with diazepam, droperidol, sufentanil, and vecuronium. The tracheal was intubated easily. Anesthesia was maintained with a sufentanil infusion (initial bolus of 0.5 $\mu g \cdot kg^{-1}$ followed by a maintenance infusion of 0.1–0.2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$), 50% nitrous oxide, and intermittent intravenous doses of diazepam (total 5 mg) and droperidol (total 2.5 mg).

The patient's condition was monitored continuously by means of an ECG, an indwelling radial arterial catheter, a 9.375-cm- (3.75-in-) long 16-g internal jugular central venous pressure (CVP) catheter (with a water manometer), a pulse oximeter, an esophageal stethoscope, an oral temperature probe, a neuromuscular stimulator, an end-tidal (ET) CO_2 and N_2 mass spectrometer (System of Anaesthetic and Respiratory Analysis [SARA]; SARA is a mass spectographic system with internal CO_2 calibration every 3 hr), and a Foley catheter. Samples were drawn intermittently from the arterial line for determination of gas tensions and from the CVP catheter for serial measurements of hematocrit, platelet counts, and coagulation studies (prothrombin time [PT], partial thromboplastin time [PTT], thrombin time [TT], fibrinogen concentration, and the direct Coombs' test). When the patient's condition was stable, he was turned to the prone position and placed on bolsters. The table was level at all times.

The patient's course was uneventful through the first 4 hr, aside from a gradual reduction in esophageal temperature from 96.8 to 94.1°F (36 to 34.5°C) despite active measures to maintain normothermia. Estimated blood loss was 400 mL to that stage; 2 U of packed red blood cells had been transfused slowly over the previous 90 min. The hematocrit at that time was 0.33 (preoperatively 0.39) and the platelet count was 118 × 10^9/L. However, the PT was prolonged to 16 sec (control 11 sec) and the PTT was 55 sec (control 30 sec). Fresh frozen plasma was ordered thawed and 2 U were promptly administered after confirmation of the prolonged PT and PTT.

Over the next hr, the patient's blood pressure decreased progressively from 80/50 mm Hg (preoperative blood pressure was 90/60 mm Hg) to 50/20 mm

---

Received from the Departments of Anesthesia and Orthopedic Surgery, University of Saskatchewan, University Hospital, Saskatoon, Saskatchewan, Canada. Accepted for publication February 27, 1989.

Address correspondence to Dr. Lang, Department of Anesthesia, University Hospital, Saskatoon, Saskatchewan, Canada S7N 0X0.

©1989 by the International Anesthesia Research Society

Hg with no change in either heart rate (60 beats/min) or rhythm. Nitrous oxide was then discontinued. CVP decreased to 9 from 14 cm H_2O but was promptly restored by giving additional blood and crystalloid solutions. Acrocyanosis was observed, but transcutaneous oxygen saturation remained above 95% ($\mathrm{Fio_2}$ 0.5 to 1.0). Arterial blood gas tensions revealed an insignificant increase in the A-a $\mathrm{Po_2}$ difference (with use of a standard formula for the estimation of alveolar $\mathrm{Po_2}$ corrected for arterial $\mathrm{Paco_2}$ [$\mathrm{Pao_2} = \mathrm{Fio_2} \times (760 - 47) - 1.25\ \mathrm{Paco_2}$] from a control of 418 to 494 mm Hg), whereas the $\mathrm{Pao_2}$ remained above 100 mm Hg. The output of urine (that was now bloody) had decreased from a control rate of 0.75 $\mathrm{ml\cdot kg^{-1}\cdot hr^{-1}}$ to near 0. The $\mathrm{ETco_2}$ concentration decreased only with the onset of hypotension (from baseline of 30 to 24 mm Hg). End-tidal N_2 changes were not recorded by the authors; the line measurements were made, but the information stored in SARA was lost before it could be retrieved. The direct Coombs' test was negative.

Pharmacologic support of the circulation was now begun with dopamine (20–30 $\mu\mathrm{g\cdot kg^{-1}\cdot min^{-1}}$). Auscultation through esophageal stethoscope revealed no adventitous sounds except those attributed to the surgical procedure; auscultation was intermittent to increase the mobility of the anesthetist. Because of his deteriorating cardiovascular status, the patient's surgical wound was rapidly closed and the patient was turned to the supine position to facilitate cardiopulmonary resuscitation. With the patient in that position, a loud gurgling murmur was now heard by auscultation over the precordium; aspiration through the central venous catheter produced blood and blood only. A tube was inserted into the right side of the chest as breath sounds were diminished on that side, but no air was present under tension in the chest. Pericardiocentesis yielded neither air nor blood. In spite of continued resuscitative efforts, the patient died.

At autopsy the next morning, the heart and pulmonary vessels were opened under water, with the release of unquantified but substantial amounts of air from the right ventricle and pulmonary artery. There were no other findings of significance.

Table 1. Differential Diagnosis of Cardiovascular Instability

- Hypovolemia
  - Absolute
    - Underestimated blood and fluid losses
    - Concealed blood loss (retroperitoneal hematoma, free peritoneal blood, pericardial or pleural blood)
  - Relative
    - Spinal shock secondary to cord trauma or traction
    - Anaphylactic or anaphylactoid reaction
    - Transfusion reaction
- Cardiomyopathy
- Mechanical Obstruction
  - Improper positioning
  - Pericardial tamponade
  - Tension pneumothorax
  - Air or fat embolism

Discussion

Although air embolism is well documented in cranial (5–10), cervical spine (10–13), and obstetric (14,15) procedures, there are no data documenting the incidence or clinical significance of embolic phenomenon in the prone position during thoracolumbar spinal surgery. However, two cases of fatal fat embolism occurring during Harrington instrumentation and spinal fusion have been well documented (16,17). Another case of fatal fat embolism with scoliosis fusion was reported in 1974 but with only scanty details (18). Although fat embolism may have contributed to the clinical picture in our patient, it was not demonstrable at autopsy.

A case of sudden cessation of cardiac output during spinal fusion in a case similar to ours was reported in 1970 (19). No adequate explanation of the events was given, but the events were compatible with venous air embolism, though the heart was not opened under water at autopsy.

A case of venous air embolism during spinal surgery detected by Doppler sonography and right atrial catheter aspiration during spinal surgery in the prone position was reported by Albin et al. (5) in 1978. However, this patient underwent extensive laminectomy from the cervical to sacral vertebra, and air embolism during cervical spine surgery is well described (10–13). More recently, Frankel and Holzman (20) reported a case of nonfatal air embolism during posterior spinal fusion in a 12-year-old girl (weight 50 kg). They reported the mass spectrographic consequences of the event (increase in $\mathrm{ETN_2}$ and decrease in $\mathrm{ETco_2}$) and semiquantitatively estimated the amount of air entrained as 35 $\mathrm{ml\cdot kg^{-1}}$—most certainly a potentially lethal volume even if grossly overestimated.

Although we postulate that the pathological process leading to cardiac arrest in our patient was the entrainment of air documented at autopsy, the antemortem differential diagnosis included a number of other possibilities. Table 1 lists some of the factors considered in explaining the low cardiac output and the coagulopathy that developed in our patient. Although the association of Duchenne muscular dystrophy and malignant hyperthermia susceptibility is recognized (17), we discounted malignant hyperthermia early because there was no evidence of a hypermetabolic state (i.e. neither the $\mathrm{ETco_2}$ or the temperature increased).

In considering what happened during anesthesia and surgery, we note that our patient remained hypotensive despite fluid resuscitation, whereas autopsy revealed no evidence of concealed blood loss, focal spinal cord trauma, or cardiomyopathy (21). A transfusion reaction was considered probable, but the direct Coombs' test was negative. Although the scaphoid chest may have been easily compressed externally during the procedure, repeated checking of the patient's position was negative, and the hemodynamic status did not improve after the patient was turned to the supine position. Pericardial tamponade and tension pneumothorax were ruled out during resuscitation. Finally, the large amounts of air in the pulmonary artery and the right ventricle at autopsy confirmed the diagnosis of air embolism.

Whereas we report fatal air embolism during spinal surgery in the prone position, it is uncertain how frequently small amounts of air entrainment might occur under these conditions and how such an outcome could be prevented. Certainly the use of full monitoring must be advocated, as well as the avoidance of nitrous oxide. However, in the presence of thoracic deformity a CVP catheter may not be optimally placed to permit diagnostic or therapeutic aspiration (22,23). The transmission of diagnostic sounds by esophageal stethoscopes is impaired by extraneous noises, and the transmission of sound by the precordial Doppler diaphragm, which is difficult to position satisfactorily in a patient such as ours, is likewise affected by surgical electrical cautery (10). End-tidal gas analysis is an effective means of monitoring for air embolism (24), as is transesophageal echocardiography (25), but they require both operational capability and a high degree of observer awareness.

In conclusion, in reporting this case of fatal air embolism associated with performance of Harrington spinal fusion, we hope to illustrate the existence of the association and to promote appropriate study and prevention in the future.

We thank David A.E. Shephard, MD for editorial assistance and Flo Welch for secretarial support.

References

1. Hofress DW. Fatal air embolism during transurethral resection. Urology 1984;131:355.
2. Michenfelder JD, Martin JT, Altenburg BM, Rehder K. Air embolism during neurosurgery. JAMA 1969;208:1353–8.
3. Harrington PR, Dickson JH. An 11 year clinical investigation of Harrington instrumentation: a preliminary report of 578 cases. Clin Orthop 1973;93:113–30.
4. Sponseller PD, Cohen MS, Nachemson AL, Hall JE, Wohl MEB. Results of surgical treatment of adults with idiopathic scoliosis. J Bone Joint Surg 1978;69 667–75.
5. Albin MS, Carroll RG, Maroon JC. Clinical considerations concerning detection of venous air embolism. Neurosurgery 1978;3:380–4.
6. Standefer M, Bay JW, Trusso R. The sitting position in neurosurgery: a retrospective analysis of 488 cases. Neurosurgery 1984;14:649–58.
7. Maroon JC, Albin MS. Air embolism diagnosed by Doppler ultrasound. Anesth Analg 1974;53:399–40.
8. Harris MM, Yemen TA, Davidson A, et al. Venous embolism during craniectomy in supine infants. Anesthesiology 1987; 67:816–9.
9. Shenkin HN, Goldfedder P. Air embolism from exposure of posterior cranial fossa in the prone position. JAMA 1969; 210:726.
10. Michenfelder JD, Miller RH. Evaluation of ultrasonic device (Doppler) for the diagnosis of venous air embolism. Anesthesiology 1972;36:164–7.
11. Higgins JW. Air embolism during neurosurgery. Br J Anaesth 1970;42:459–62.
12. Scoville WB. Soft cervical disc herniation. Neurosurgery 1978; 2:187–8.
13. Humphreys RP, Creighton RE, Hendrick EB, Hoffman HJ. Advantages of the prone position for neurosurgical procedures of the upper cervical spine and posterior cranial fossa in children. Childs Brain 1975;1:325–35.
14. Malinow AM, Naulty JS, Datta S, Hunt CO, Ostheimer GW. Precordial ultrasonic doppler monitoring during cesarean delivery. Anesthesiology 1985;63:A432.
15. Younker D, Rodriguez V, Kavanaugh J. Massive air embolism during cesarean section. Anesthesiology 1986;65:77–9.
16. Gittman JE, Buchanan TA, Fisher BJ, Bergeson PS, Palmer PE. Fatal fat embolism after spinal fusion for scoliosis. JAMA 1983;249:779–81.
17. Sethna NF, Rockoff MA, Worthen M, Rosnow JM. Anesthesia-related complications in children with Duchenne muscular dystrophy. Anesthesiology 1988;68:462–5.
18. Brown LP, Stelling FH. Fat embolism as a complication of scoliosis fusion. J Bone Joint Surg 1974;56:1764.
19. Dykes HM, Fuller JE, Goldstein LA. Sudden cessation of cardiac output during spinal fusion. Anesth Analg 1970;49: 596–9.
20. Frankel AH, Holzman RS. Air embolism during posterior spinal fusion. Can J Anaesth 1988;35:511–4.
21. Perloff JK, deLeon AC Jr, O'Doherty D. The cardiomyopathy of progressive muscular dystrophy. Circulation 1966;33:625–48.
22. Colley PS, Artu AA. Bunegin-Albin catheter improves air retrieval and resuscitation from lethal venous air embolism in dogs. Anesth Analg 1987;66:991–4.
23. Bunegin L, Albin MS, Helsel PE, Hoffman A, TinpKan Hung. Positioning the right atrial catheter: a model for reappraisal. Anesthesiology 1981;55:343–8.
24. Drummond JC, Prestow RJ, Scheller MD. The relative sensitivities of pulmonary artery pressure, end-tidal CO_2, and end-tidal N_2 analysis in the detection of venous air embolism. Anesthesiology 1984;61:A338.
25. Furuya H, Suzuki T, Okumura F, Kishi Y, Uefuji T. Detection of air embolism by transesophageal echocardiography. Anesthesiology 1983;58:124–9.

Letters to the Editor

An Inexpensive, Disposable Adapter for Increasing the Safety of Blind Nasotracheal Intubations

To the Editor:

Complications that may involve the patient during blind nasal intubation of the trachea include trauma to the nasal passage, sinusitis (1), bacteremia (2), and submucosal dissection of the nasopharynx (3). Little attention has been paid to possible complications involving the anesthetist performing the intubation. Successful intubation may be heralded by a stream of upper airway secretions, often blood tinged. With the recent isolation of human immunodeficiency virus in saliva as well as blood, this source of health worker risk is real (4).

Donenfeld (5) has described an aid to blind nasotracheal intubation that involves the use of the distal end of the anesthesiologist's ear piece tubing placed loosely inside the endotracheal tube. This procedure decreases the risk of infection to the anesthetist but requires that a piece of specialized equipment be present and, thereby, poses the risk of patient cross-contamination when using the same equipment in different patients.

We recently adapted our technique for blind nasal intubation by the addition of a simple, inexpensive heat and moisture exchanger (HME) (Humid-Vent 1, Gibeck Respiration, Sweden) on the proximal end of the endotracheal tube (Fig. 1). This disposable device effectively creates a trap for respiratory secretions if the patient should cough or exhale vigorously. We have used this technique on multiple patients over the last year and found it to be most effective in preventing the anesthetist from receiving an earful of secretions. The small size of the HME makes it an easy addition to our emergency resuscitation kit.

The character of the breath sounds is changed somewhat by the device and becomes more whistling in nature. The resistance to flow offered by the heat and moisture exchanger is minimal (6) and has not interfered with recognition of breath sounds emanating from the tube. The efficacy of the device to trap very small particles is unknown and thus careful attention to good technique remains mandatory.

Michael J. Dorsey, MD
Brian R. Jones, MD
Department of Anesthesiology
University of California, San Diego
San Diego, CA 92103

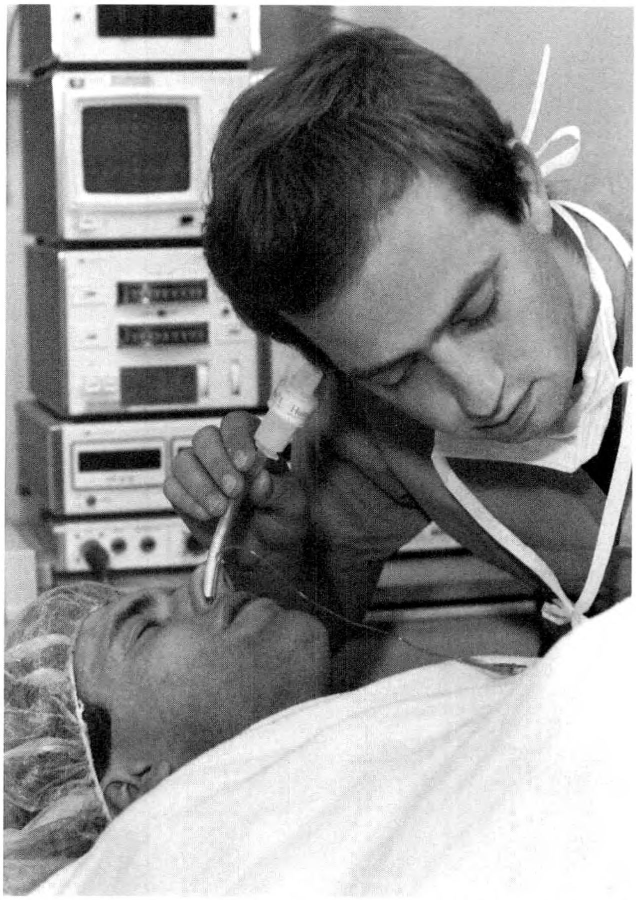


Figure 1. The disposable heat and moisture exchanger (Humid-Vent 1) attached to an endotracheal tube during blind nasotracheal intubation.

References

1. Arens JF, LeJeune FE, Webre DR. Maxillary sinusitis, a complication of nasotracheal intubation. Anesthesiology 1974;40:415.
2. Dinner M, Tjeuw M, Artusio JF. Bacteremia as a complication of nasotracheal intubation. Anesth Analg 1987;66:460–2.
3. Daly WM. Unusual complication of nasal intubation: report of a case. Anesthesiology 1953;14:96.
4. Groopman JE, Salahuddin SZ, Sarngadharan MG, et al. HTLV-III in saliva of people with AIDS related complex and healthy homosexual men at risk for AIDS. Science 1984;226:447–51.
5. Donenfeld RF. A technique to aid blind nasotracheal intubation. Anesth Analg 1987;66:283–4.
6. Shelly M, Bethune DW, Latimer RD. A comparison of five heat and moisture exchangers. Anaesthesia 1986;41:527–32.

©1989 by the International Anesthesia Research Society

Multiple Nerve Palsies after Anesthesia—A Complication of Nitrous Oxide Use?

To the Editor:

Navalgund et al. (1) report an interesting case involving a 30-year-old diabetic man who underwent pancreatic transplantation during a 9.5-hr general anesthetic that included nitrous oxide. As he awakened from the anesthetic, it was noted that he had severe peripheral polyneuropathy involving the nerves of the distal upper extremities documented by electromyography. Throughout their report, the authors emphasize the importance of positioning patients during anesthesia and surgery and its importance in the generation of anesthetic induced neuropathy, and offer as differential diagnoses for etiology of the neuropathy "mononeuritis multiplex and interstitial fluid accumulation during prolonged time and immobility."

Clinical description of the patient by Navalgund et al. (1) is not consistent with that of the syndrome of mononeuritis multiplex, which is generally very painful and typically involves a major nerve trunk. The diabetic neuropathic picture that they describe is actually more characteristic of the more common diabetic polyneuropathy affecting the distal extremities symmetrically, usually the feet and legs more than the hands, sometimes with motor changes. The etiology of diabetic polyneuropathy, although still unknown, probably results from metabolic abnormalities in nerve tissue. The polyol pathway, through aldosereductase, is believed to be stimulated by persistent hyperglycemia leading to intracellular accumulation of sorbitol and osmotic swelling of cells. Hypothesized contributing subcellular activities include inhibition of myo-inositol uptake, altered phosphoinositide metabolism, reduction in sodium-potassium-ATPase activity mediated by protein C kinase, and axo-glial dysjunction leading to abnormal nerve conduction (2). Treatment of patients with diabetic neuropathy with the aldose-reductase inhibitor sorbinil, although not affecting intracellular myo-inositol, has resulted in reduction of intraneural accumulation of sorbitol and fructose. This reduction was associated with regeneration of myelinated fibers and improvement in nerve conduction (3,4).

The authors failed to take into account in their differential diagnoses a very important cause of peripheral neuropathy that may occur after anesthesia. This patient had a 9.5-hr nitrous oxide anesthetic (concentration unreported), followed by a severe, distal, symmetrical sensorimotor neuropathy. Nitrous oxide causes neuropathy because of its inactivation of vitamin B_{12} by oxidation (5) and is similar to the neuropathy of pernicious anemia. This condition involves the spinal cord (posterior and lateral column degeneration), peripheral nerves, and the cerebellum (6). Clinically, weakness and paresthesias (distal and symmetrical) are noted first, followed by ataxia, loss of vibration sense, and spasticity and motor weakness. Electrophysiologic testing (electromyogram and nerve conduction velocity) reveals axonal sensorimotor polyneuropathy with distal denervation. Sural nerve biopsy shows rare fibers with degenerating myelin.

Although neuropathy has not been reported in healthy patients after brief exposures to nitrous oxide, prolonged or repeated exposures may lead to neuropathic changes (7,8). Patients who are susceptible, however, have demonstrated manifestations of nitrous oxide toxicity with exposures shorter (9) than those in the case described by Navalgund et al. (1). Schilling (10) described two patients with subclinical vitamin B_{12} deficiency who developed polyneuropathy after exposure to nitrous oxide for 90 min. Layzer (8) noted that patients chronically exposed to nitrous oxide developed sensorimotor polyneuropathy with loss of small-muscle hand coordination, a finding noted in the patient described by Navalgund and coworkers. The propensity of certain patients to develop neurotoxicity, therefore, is influenced by their susceptibility. Patients with gastrointestinal abnormalities leading to poor vitamin B_{12} or folate absorption would be expected to be particularly susceptible. Drugs may cause megaloblastic anemia through their interference with DNA synthesis or folate antagonism (6,11).

Because nitrous oxide is harmful to susceptible patients with as little as 2 hr of exposure (9,10) and may cause neuropathy unresponsive to treatment after longer term exposure (8), it is wise to avoid nitrous oxide in patients with possible vitamin B_{12} or folate deficiencies, including patients with malabsorption syndromes and patients on chemotherapeutic drugs that inhibit DNA synthesis (alkylating agents, nucleotide analogues, and others) or folate antagonists. Certain anticonvulsants (phenytoin, primidone, and phenobarbital) have also been implicated in mildly disturbing folate metabolism or absorption (6). It would be interesting to know whether the patient described by Navalgund et al. (1) had any other signs of B_{12} deficiency, such as megaloblastosis, and the concentration of nitrous oxide given to their patient.

Benjamin A. Lampert, MD
Department of Anesthesiology
St. John's Regional Health Center
Springfield, MO

References

1. Navalgund AA, Jahr JS, Gieraerts R, Chang [illegible]-L, Garla PGN. Multiple nerve palsies after anesthesia and surgery. Anesth Analg 1988; 67:1002–4.
2. Asbury AK. Understanding diabetic neuropathy. N Engl J Med 1988; 319:577–8.
3. Dyck PJ, Zimmerman BR, Vilen TH, et al. Nerve glucose, fructose, sorbitol, myo-inositol, and fiber degeneration and regeneration in diabetic neuropathy. N Engl J Med 1988;319:542–8.
4. Sime AAF, Bril V, Nathaniel V, et al Regeneration and repair of myelinated fibers in sural-nerve biopsy specimens from patients with diabetic neuropathy treated with sorbinil. N Engl J Med 1988;319:548–55.
5. Banks RGS, Henderson RJ, Pratt JM. Reactions of gases in solution III. Some reactions of nitrous oxide with transition metal complexes. J Chem Soc Sec (A) 1968;3:2886–90.
6. Babio BM, Bunn HF. Megaloblastic anemias. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, and Wilson JD, eds. Harrison's Principles of Internal Medicine, 10th ed. New York: McGraw-Hill, 1983:1853–60.

7. Sahen KZ, Mendell JR, Couri D, et al. Polyneuropathy from inhalation of N_2O cartridges through a whipped-cream dispenser. Neurology 1978;28:485–7.
8. Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. Lancet 1978;2:1227–30.
9. Amos RJ, Amess JAL, Hinds CJ, Mollin DL. Incidence and pathogenesis of acute megaloblastic bone-marrow change in patients receiving intensive care. Lancet 1982;8303:835–9.
10. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B_{12} deficient subjects? JAMA 1986;255:1605–6.
11. Wickramasinghe SN. Effect of azathioprine on the cell cycle of haematopoietic cells. Scand J Haematol 1976;16:38–40.

In Response:

We thank Dr. Lampert for his interest in our report of a case of multiple nerve palsies after anesthesia and surgery (1). As Dr. Lampert states, nitrous oxide neuropathy has been reported to occur in healthy persons after repeated exposures (2–5) and in susceptible patients after shorter exposures (6–7). Our patient was given 50% nitrous oxide during pancreatic transplantation, which lasted 9.5 hr. The presence of multiple nerve dysfunction was noted very soon after anesthesia. The patients described by Amos et al. (6) had a history of megaloblastic anemia. Shilling's patients had subclinical vitamin B_{12} deficiency and later developed polyneuropathy after exposure to nitrous oxide for 90 minutes (7). Our patient had no malabsorption syndrome leading to deficiency of vitamin B_{12} or folate. In fact, his hemoglobin (144 g/L) and hematocrit (0.42) were unusually high for a patient with history of chronic renal failure. His mean corpuscular volume was 78 fentoliter and mean corpuscular hemoglobin 26 pg, indicating microcytosis and hypochromia. He was receiving no chemotherapeutic agents that inhibit DNA synthesis, such as alkylating agents or folate antagonists. Moreover, our patient has been anesthetized on eight occasions since his pancreatic transplantation and has had more than 16 hr of exposure to nitrous oxide in concentrations from 50% to 60%. No adverse effect of nitrous oxide was observed after these exposures, and the patient's motor function continued to improve.

In summary, the lack of any evidence of susceptibility to nitrous oxide toxicity in our patient and the almost immediate appearance of nerve dysfunction after a single exposure make nitrous oxide an unlikely cause of his polyneuropathy.

Ashok A. Navalgund, MD
Jonathan Jahr, MD
Roland Gieraerts, MD
Juei-Ling Chang, MD
Glenn S. Price, MD
Department of Anesthesiology and
Critical Care Medicine,
University of Pittsburgh
School of Medicine
Pittsburgh, PA 15261
P. G. N. Garla, MD
Loyola University Medical Center
Maywood, IL 60153

References

1. Navalgund AA, Jahr JS, Gieraerts R, Chang J-L, Garla PGN. Multiple nerve palsies after anesthesia and surgery. Anesth Analg 1988;67:1002–4.
2. Sahenk Z, Mendell HR, Couri D, et al. Polyneuropathy from inhalation of N_2O cartridges through a whipped-cream dispenser. Neurology 1978; 28:485–7.
3. Blanco G, Peters HA. Myeloneuropathy and macrocytosis associated with nitrous oxide abuse. Arch Neurol 1983;40:416–8.
4. Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. Lancet 1978;2:1227–30.
5. Hayden PJ, Hartemink RJ, Nicholson GA. Myeloneuropathy due to nitrous oxide. Burns 1982;9:267–70.
6. Amos RJ, Amess JAL, Hinds CJ, Mollin DL. Incidence and pathogenisis of acute megaloblastic bone-marrow change in patients receiving intensive care. Lancet 1982;8303:835–9.
7. Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B12 deficient subjects? JAMA 1986;255:1605–6.

Imprecise Fentanyl and Sufentanil Labels

To the Editor:

We have noted that fentanyl and sufentanil ampules consistently contain 10%–20% more of the agent than the ampules' labels indicate. Many of us are aware of this discrepancy and know that an additional amount is present in ampules of single dose vials of many other drugs as well. Although this additional volume and dosage may be of little clinical significance with many drugs, this cannot be said of these extremely potent narcotics. We think that this excess amount could have grave clinical significance.

In Figure 1, the A arrows indicate that the syringe plunger is at the 10- or 3-mL mark of the 10- and 3-mL Becton Dickinson & Co. syringes respectively. With each 10- and 3-mL syringe, the B arrow indicates the level of the narcotic solution after the entire contents of a 5- or 2-mL ampule (according to the ampules' labels) respectively have been aspirated into the syringe. The distance between arrows A and B represents the volume of narcotic solution. In the figure, the two vials on the left have labels stating that they contain "5 mL" and "250 μg/5 mL." The two vials on the right have labels stating that they contain "2 mL" and "100 μg/2 mL." In addition, all of the vials' labels state "50 μg/mL." As can be seen by observing the differences between the A and B arrows, all four ampules contained a volume of narcotic solution in excess of the manufacturer's claim as printed on the labels. Because the concentration is stated on each ampule as 50 μg/mL, we conclude that this extra volume of narcotic solution represents an additional number of micrograms of potent narcotic. If two or more vials are drawn up in one syringe, as is common practice, the excess volume increases proportionally. Sleep and/or ventilatory insufficiency may be induced by the excess of drug alone, even in a healthy adult.

This observation raises several issues in clinical practice:

1) Is it appropriate and safe for ampules of such potent respiratory depressants to be labeled inaccurately?
2) Does not this excess dosage give the drug abuser a source of narcotics?
3) Should this discrepancy be changed by the manufacturer?

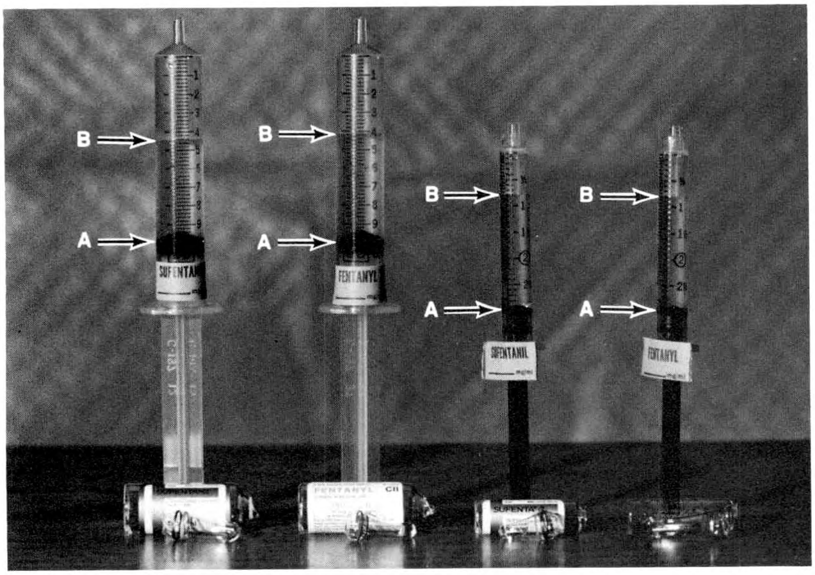


Figure 1. **A** indicates the 10- or 3-mL marking of the 10- and 3-mL syringes. **B** indicates the level of the narcotic solution in each syringe. By observing the difference between the arrows of any particular syringe, the volume of the narcotic solution can be ascertained.

4) In the meantime, what should be done with this extra volume of drug? Is it simply disposed of when drawn up? If so, what about accountability of narcotics? If given, is the excess drug charted on the anesthesia record; and, if so, how is this amount reconciled with the narcotic record (which shows only the ampules' labeled volume as dispensed)?

We are interested in knowing readers' views on these issues and, in particular, what they do with this excess narcotic.

Robert W. Kennedy, MD
William Till, MD
Jagdip B. Shah, MD
Department of Anesthesiology
Louisiana State University Medical Center
1501 Kings Highway
Box 067
Shreveport, LA 71130

Perioperative Cardiovascular Collapse in a Patient Previously Treated with Doxorubicin

To the Editor:

The report by Borgeat et al. (1) nicely documents intraoperative cardiovascular decompensation in a patient previously treated with doxorubicin. However, Borgeat and colleagues (1) are misinformed about the lack of previous reports of interactions between anesthetics and doxorubicin. Cardiovascular complications and death have been reported intraoperatively and in the immediate postoperative period after the administration of anesthetics in patients receiving anthracyclines (doxorubicin and daunorubicin) (2–6). In a review of anesthetic records from one institution in 68 patients with a history of anthracycline drug therapy, Burrows et al. (4) identified a history of congestive heart failure as a risk factor for intraoperative cardiovascular complications. Eight patients developed intraoperative hypotension. In two of these patients, monitored with intraarterial and pulmonary artery catheters during the hypotension, which required pressor support, exacerbation of primary myocardial dysfunction was documented as the cause of the cardiovascular decompensation, presumably due to anthracycline cardiomyopathy.

The patient reported by Borgeat et al. (1) indeed had a history of congestive heart failure preoperatively and thus was at risk for the cardiovascular complications reported. When anesthesiologists evaluate these patients preoperatively, it is important that any history of congestive heart failure be recognized as a risk factor for sudden and unpredictable intraoperative cardiovascular decompensation.

Paul R. Hickey, MD
Department of Anesthesia
Harvard Medical School and The Children's Hospital
300 Longwood Avenue
Boston, MA 02115

References

1. Borgeat A, Chiolero R, Baylon P, Freeman J, Neff R. Perioperative cardiovascular collapse in a patient previously treated with doxorubicin. Anesth Analg 1988;67:1189–91.
2. Smith RM, DasGupta V. Adriamycin cardiotoxicity. Anesthesiology Rev 1981;8:14–9.
3. Caviale P, McClellan EL. Adriamycin toxicity: effect in subsequent anesthesia and surgery. J Kans Med Soc 1981;82:553–4.
4. Burrows FA, Hickey PR, Colan S. Perioperative complications in patients with anthracycline chemotherapeutic agents. Can Anaesth Soc J 1985; 32:149–57.
5. McQuillan PJ, Morgan BA, Ramwell J. Adriamycin cardiomyopathy. Fatal outcome of general anesthesia in a child with adriamycin cardiomyopathy. Anaesthesia 1988;43:301–4.
6. Jonsson T, Mortensen SA, Aabo K. Acute cardiac failure precipitated by anesthesia and surgery in patients treated with adriamycin. Ugeskr Laeger 1984;146:3837–9.

In Response:

The appearance of a severe perioperative left ventricular dysfunction in a patient previously treated with doxorubicin, prompted us to make a medline literature search for a combined or synergic cardiodepressor effect between doxorubicin and anesthetic agents, being aware of the cardiodepressing effects of each substance (1,2). However, we thank Dr. Hickey for giving us the opportunity to obtain more information about doxorubicin and anesthesia as for unknown reasons the papers from Burrows et al. (3), and Caviale et al. (4) were not quoted on our computer research. Nevertheless, we completely agree with the fact that any history of heart failure in patients previously treated with doxorubicin should be recognized as a risk factor for sudden intraoperative cardiovascular decompensation during general anesthesia. Moreover, we would like to emphasize how insidious and unpredictable manifestations of doxorubicin cardiomyopathy can be during general anesthesia. Burrows et al. (3) in a retrospective review, described two episodes of intraoperative hypotension attributed to an interaction between doxorubicin cardiomyopathy and anesthesia. These patients were in severe heart failure (NYHA III and IV) taking digoxin, diuretics, and vasodilators; however, our patient, who was leading a normal life, was taking neither cardiotonics, diuretics, nor vasodilators. Her only complaint was of a slight dyspnea (NYHA I or II). Nevertheless, she suffered a severe left ventricular failure during general anesthesia.

Our case report illustrates that the anesthesiologists should be ready to cope with any cardiovascular decompensation during general anesthesia, in view of a patient previously treated with anthracyclines with or without a history of heart failure.

A. Borgeat, MD
Department of Anesthesia
Centre Hospitalier Universitaire Vaudois (CHUV)
1011 Lausanne Switzerland

References

1. Minow RA, Benjamin RS, Lee ET. Adriamycine cardiomyopathy-risk factors. Cancer 1977;39:1397–402.
2. Sonntag H, Donnath U, Hillebrand W, Merin RG, Radke J. Left ventricular function in conscious man and during halothane anesthesia. Anesthesiology 1978;48:320–4.
3. Burrows FA, Hickey PR, Colan S. Perioperative complications in patients with anthracycline chemotherapeutic agents. Can Anaesth Soc J 1985; 32:149–57.
4. Caviale P, McClellan EL. Adriamycin toxicity: effect in subsequent anesthesia and surgery. J Kans Med Sco 1981;82:553–4.

Heart Synchronized Ventilation during Extracorporeal Shock Wave Lithotripsy

To the Editor:

Drs. Jansson et al. describe in their article on heart synchronized ventilation an interesting new mode of ventilation for patients undergoing general anesthesia for extracorporeal shock wave lithotripsy (ESWL) (1). They fail, however, to stress one of the main advantages of such heart triggered ventilation.

We have also employed this ventilatory mode in 16 patients undergoing general anesthesia for ESWL (2). In our technique, the mechanical breath (3 mL/kg) starts 50–100 msec after the shock wave is fired and ends 20–50 msec before the beginning of the next QRS complex and shock wave (Figure 1). Absence of motion of the stone during shock wave delivery is the true advantage of this method rather than the minimization of movements of the stone during ventilation as with the technique described by Jansson, et al. Directing the shock waves to the stone by the urologist can be achieved easily and accurately during a brief period of apnea.

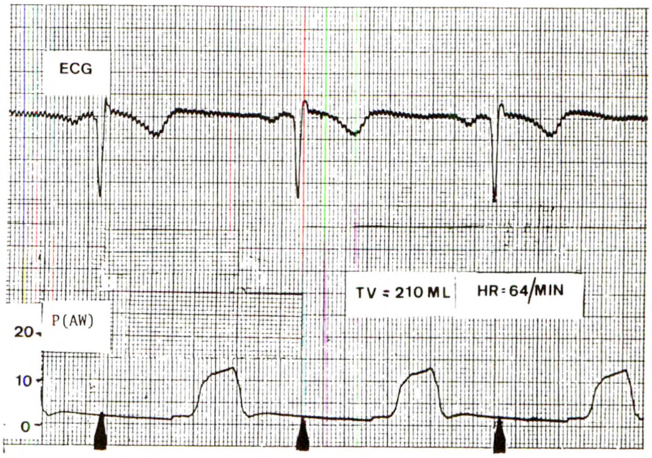


Figure 1. Simultaneous recording of ECG and airway pressure (Paw) in a patient undergoing general anesthesia for ESWL with QRS-activated positive pressure ventilation. Black triangles indicate shockwaves. Note that shockwaves always occur during apnea at functional residual capacity.

Eran Segal, MD
Azriel Perel, MD
Department of Anesthesiology
Sheba Medical Center
Tel–Hashomer
Israel

References

1. Jansson L, Bengtsson M, Carlsson C. Heart synchronized ventilation during general anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 1988;67:706–9.
2. Perel A, Mahler Y, Mager M, Segal E, Podeh D, Davidson JT. QRS-activated positive pressure ventilation for true stone motionlessness during extracorporeal shock wave lithotripsy (ESWL). Crit Care Med 1987;15:398 (abst). J Clin Anesth (in press).

Nitroglycerine, Succinylcholine and Intraocular Pressure

To the Editor:

In a recent article (1), it was shown that the response of intraocular pressure (IOP) to succinylcholine used for tracheal intubation could be abolished by pretreatment with nitroglycerine (NTG). We have investigated whether this finding was reproducible in an experimental porcine model.

Five piglets (24–26 kg) were anesthetized (piritramide 0.1 mg·kg^{-1}·h^{-1}, pancuronium 0.04 mg·kg^{-1}·h^{-1}, Fi_{N_2O}

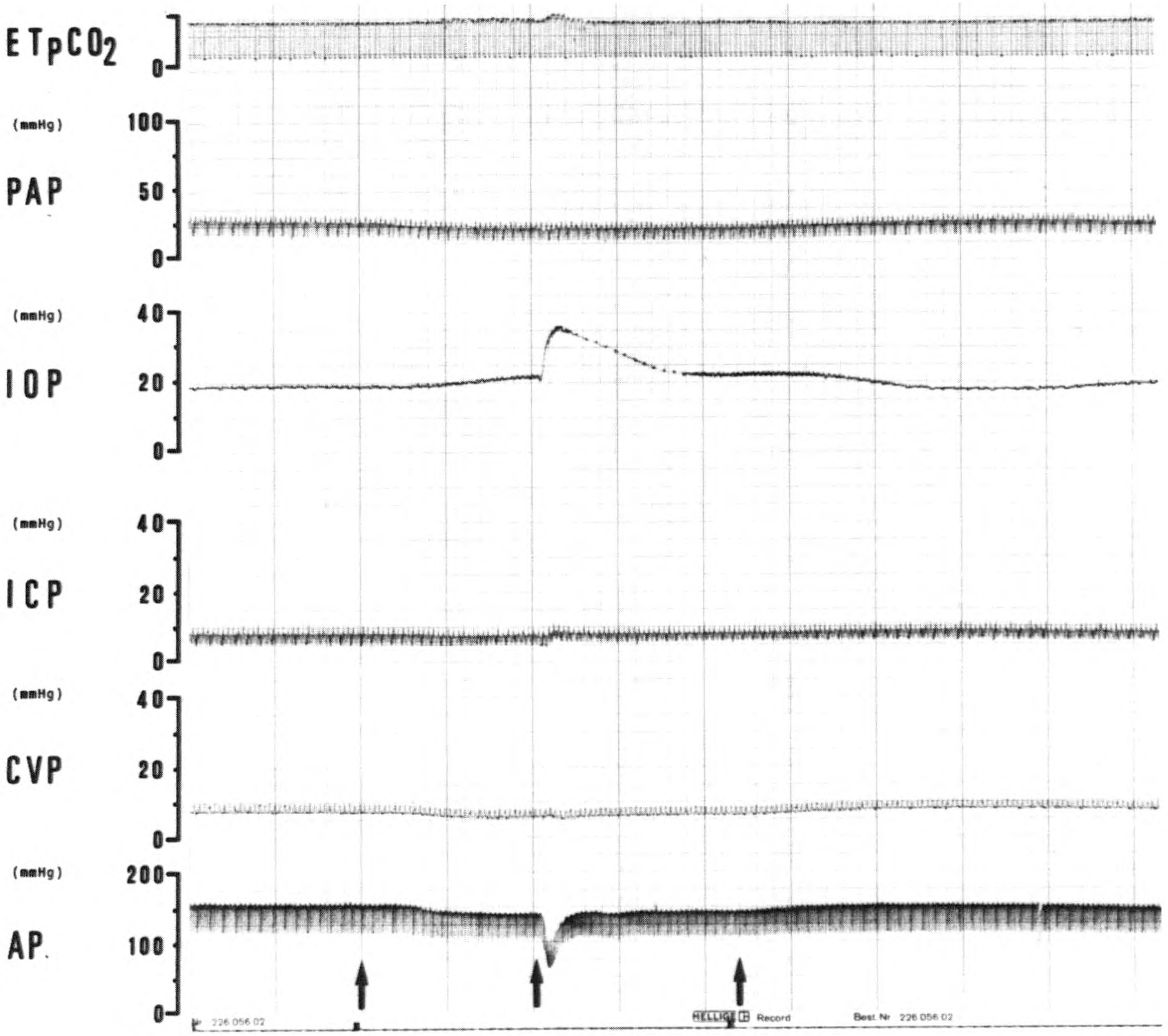


Figure 1. Effects of nitroglycerine (NTG) and succinylcholine (Sch) on end-tidal CO_2 ($EtPCO_2$), pulmonary artery pressure (PAP), intraocular pressure (IOP), intracranial pressure (ICP), central venous pressure (CVP), and arterial blood pressure (AP). 1st marker, start of NTG infusion; 2nd marker, administration of Sch; 3rd marker, termination of NTG. (Original recording, chart speed = 0.25 mm·sec^{-1}.)

0.6), intubated, and instrumented (arterial catheter [thoracic aorta], pulmonary artery catheter, cerebral ventricle cannula). Ventilation was monitored by end-tidal capnometry ($Et[CO_2] \approx 4.5\%$). IOP was measured directly with a 22G Teflon cannula inserted into the right anterior chamber (2).

In our model, intranasal NTG solution (2 mg/3 mL, 1.5 mL in each nostril) given 3–4 hr after intubation to unstimulated pigs did not affect the arterial blood pressure or IOP curves. NTG was therefore administered intravenously at a rate of 2 mg·kg^{-1}·h^{-1}. Effects are shown in Figure 1 (between 1st and 2nd markers). Succinylcholine was then administered at a dosage of 1.5 mg·kg^{-1} (Figure 1, 2nd marker). The 3rd marker indicates termination of the NTG infusion.

The course of the recorded variables as shown in Figure 1 was reproducible in all five pigs.

We do not believe that the results reported by Mahajan et al. are universally applicable. Whether this is because of species differences, differences in methods (direct vs indirect IOP measurement, experimental vs clinical setting), or other reasons requires further investigation.

Lastly, we wonder how Mahajan et al. could obtain mean IOP data to one second decimal point (e.g., 13.86 ± 0.82 in their Table 1). This could not be possible with an applanation tonometer, an instrument with an accuracy of ±0.5 mm Hg. We conclude that the succinylcholine controversy is not yet exhausted.

J. P. Jantzen, MD
H. J. Hennes, MD
T. Wallenfang, MD
Departments of Anaesthesiology and Neurosurgery
Johannes Gutenberg University Medical School
Mainz, F.R. Germany

References

1. Mahajan RP, Grover VK, Sharma SL, Singh H. Intranasal nitroglycerine and intraocular pressure during general anesthesia. Anesth Analg 1988; 67:631–6.
2. Jantzen JP, Earnshaw G, Hackett GH, Hilley DM, Giesecke AH. Effects of neuromuscular blocking drugs on intraocular pressure. Anaesthesist 1987;36:223–7.

In Response:

We thank Jantzen et al. for their interest in our article on intranasal nitroglycerin and intraocular pressure during general anesthesia (1). After carefully reviewing their comments, we feel that the controversy in results could be due to species difference. Nitroglycerin (NTG) is a direct acting relaxant of smooth muscle and is known to cause significant decreases in systemic arterial pressure (2,3), central venous pressure, and pulmonary artery pressure (4,5). We also observed a significant decrease in mean arterial pressure and central venous pressure with NTG in our study (1). In addition NTG increases intracranial pressure (6). Jantzen et al. in their study observed no changes in either intraocular pressure (IOP) or in any of the other parameters, even with a continuous infusion of NTG. They observed an increase in IOP with succinylcholine, as we observed an increase in IOP with succinylcholine, but the increase was significantly less in our patients. In another study we observed the efficacy of even smaller doses of intranasal NTG (0.75 mg) in ameliorating pressor responses to laryngoscopy and tracheal intubation (7).

Lastly, we agree with Jantzen et al. that individual readings of IOP cannot be recorded to the second decimal point with an instrument of an accuracy of ±0.5 mm Hg; but they have probably confused the individual IOP reading with the mean IOP. It is a matter of simple arithmetic calculation that when the sum of IOP readings is divided by the total number of cases to get the mean IOP, it can result in figures with 2 or more decimal points. However, for ease of presenting data we have reported only to the second decimal point.

V. K. Grover, MD, MNAMS
Suman Sharma, MD
Department of Anesthesiology
Postgraduate Institute of Medical
Education and Research,
Chandigarh, India

References

1. Mahajan RP, Grover VK, Sharma SL, Singh H. Intranasal nitroglycerine and intraocular pressure during general anesthesia. Anesth Analg 1988; 67:631–6.
2. Christensson B, Nordenfelt I, Westling H, et al. Intravenous infusion of nitroglycerine in normal subjects. Scand J Clin Lab Invest 1969;23:49–53.
3. Armstrong PW, Armstrong JA, Marks GS. Blood levels after sublingual nitroglycerine. Circulation 1979;59:585–8.
4. Mason DT, Zelis R, Amsterdam EA. Action of the nitrites on the peripheral circulation and myocardial oxygen consumption: significance in the relief of angina pectoris. Chest 1971;59:296–305.
5. Mason DT, Braunwald E. The effects of nitroglycerin and amylnitrite on arteriolar and venous tone in human forearm. Circulation 1965;32: 755–6.
6. Morris PJ, Todd M, Philbin D. Changes in canine intracranial pressure in response to infusions of sodium nitroprusside and trinitroglycerin. Br J Anaesth 1982;54:991–6.
7. Grover VK, Sharma S, Mahajan RP. Low dose intranasal nitroglycerine attenuates pressor response. Anesthesiology 1987;66:722.

Smithisms

To the Editor:

For almost 40 years, I have been endeavoring to instill in the minds of interns and residents memorable phrases or thoughts to help them remember useful information and techniques. A few have been entitled "Smithisms." I offer some of them to my fellow anesthesiologists, and those in training, with the thought that they may in some small way contribute to bettering one's life and work and perhaps save a life. For example:

When doing a difficult spinal, epidural or intubation, concentrate only on your task; ignore everything else.

When intubating, make haste slowly.

When inducing anesthesia in children, and especially infants, airway obstruction is usually caused by soft tissues and is usually relieved by slight positive pressure on the breathing bag during inspiration, thus avoiding the laryngospasm associated with oropharyngeal airways.

When using thiopental and succinylcholine for rapid-sequence induction, wait long enough for the combination to be completely effective.

When dealing with poor-risk patients, remember how porcupines make love—gently, very gently.

How can one administer an intelligent anesthesia without knowing what is going on at "the other end of the table"? Drapes attached to the IV poles obscure one of the most valuable sources of information, the surgical procedure.

The most important object in the operating room is the patient, not the machinery attached to him.

For all its faults, the human brain is still the most reliable computer available.

Use small-bore IV needles in awake patients; use large-bore needles in sleeping patients.

Sloppiness is the best way to get into trouble, especially in emergency situations. Be neat!

General anesthesia is induced, controlled, short term coma. The antidote to coma is pain, i.e., surgery. Use one to control the other.

Attempting to topically anesthetize a *moist* mucous membrane is akin to voiding in the ocean to alter the salinity; IV scopolamine is still the best agent to dry mucous membranes so that the anesthetic agent is more effective.

Don't sell nurse anesthetists short. Even experienced anesthesiologists can glean valuable pearls from a nurse anesthetist's experience.

Try clearing your throat by fully extending your neck and trying to swallow. This is what some people expect of half-awake patients.

The best way to obstruct a toothless infant's airway is to pull up on the mandible.

Anesthesiologists and surgeons must work as partners, not as adversaries.

Muscle relaxants are too frequently used to disguise an insecure anesthesiologist's ineptitude.

If you're working hard at "anesthesia," perhaps you are doing something wrong. "Anesthesia" by an expert usually looks easy.

If you treat *every* case, even the simplest, as if it were the most difficult you ever did, you are less likely to get into trouble.

Drugs and procedures cycle. Today's new advances in drugs or techniques will probably be forgotten or contraindicated tomorrow.

If you discover a new technique, you can usually figure someone else has already discarded it.

Graduating from a famous university or hospital doesn't make you any more intelligent; it only makes you think you are.

When intubating and you cannot find the glottis, sometimes using the right hand to move the thyroid cartilage back and forth in a lateral movement several times will frequently reveal the glottis.

When inserting an endotracheal tube, it is useful to rotate it very rapidly 90° anticlockwise and then 90° clockwise as it passes between the cords.

Experience is what you have left after you've made a lot of mistakes.

Yawning under spinal anesthesia may be a symptom of hypoxia.

It is much easier and safer to give multiple small doses of drugs intravenously than it is to get the drug out. Give IV drugs in small amounts and observe the patient each time.

A kind word, given with confidence, is better than 25 mg of diazepam.

A good surgeon deserves a good anesthesiologist; a poor surgeon needs one.

Some surgeons use retractors to keep the wound from healing before they are finished with the operation.

The key to starting IVs is patience. Leaving a tourniquet on an extra 2 min makes a world of difference.

When trying to judge blood loss, the last person to ask is the surgeon.

Noisy breathing is obstructed breathing, but obstructed breathing may not be noisy.

Heavy smokers have much to cough up.

When looking directly at the easier way to do a thing, especially for long periods, you will not see it.

An ounce of application is worth a pound of abstraction.

The three requirements of a good anesthesiologist: A big tube in the trachea; a big needle in a vein; and a roll of adhesive tape.

If he had one Betz cell, he'd have a foreign body reaction.

Complications vary inversely with the skill of the anesthesiologist.

If a 9- or 10-mm tube should kink during a procedure, you can usually push a 7- or 7.5-mm tube, uncuffed and lubricated, through the lumen of the kinked area in the tube.

Ray T. Smith, Jr., MD
Department of Anesthesiology
Baystate Medical Center
Springfield, Massachusetts

Limit(ation)s for ACT

To the Editor:

Seldom do clinical tests of coagulation provide the degree of precision advocated by Gravlee et al. (1). Three problems exist with measurement of activated coagulation times (ACT) in the clinical setting. First, the most widely used mechanical ACT device and the one used in their study (Hemochron, International Technidyne Corporation, Edison, New Jersey) is provided without a standard with which to verify that the device is working properly on a day-to-day basis (timer, constant temperature, detector, consistent rotation, etc). The reagent, diatomaceous earth, is a naturally occurring substance with lot-to-lot variability and may change reactivity over time. Published control values and range of normals performed by the manufacturer on a lot-to-lot basis regularly over time are not available. In fact, since the studies by Young (2), there has been at least one change in the reagent supplied by the company (3). In the absence of company-provided standards, operators are encouraged to establish their own controls and expected range of normals. This kind of quality control and standardization is seldom, if ever, done outside the laboratory. Thus, the term "baseline" or "control" is applied to the first number obtained from the patient and used as a reference. Knowing what a "normal" value is would enhance our accuracy of determining the beginning status of the patient's coagulation as well as the reliability of the test.

Second, strict adherence to technique for reproducible results is mandatory. In visiting a number of institutions we have noticed there is virtually no standard technique in operating rooms. The volume injected, degree of agitation prior to insertion, when the timer is started and temperature of the tube, blood, and device varied in combination and degree. For example, using the same patients; blood, starting with the device and tubes at 17.2°C (room temp), a control value was 162 sec. With the device pre-warmed and the tube at room temp, the value was 146 sec. With both tube and device pre-warmed, the value was 110 sec (coefficient of variation on duplicate samples was 1.2 to 2.2%). Similar discrepancies can be shown with different degrees of agitation.

Third, changes in the patient population may alter the results. The data from Gravlee et al. show significantly lower post-protamine than pre-heparin values. Although patients were excluded if they had been given heparin in the preceding 12 hours, the data strongly suggest heparin effect. Our retrospective clinical data (Table 1) are similar

Table 1. Clinical Data

	ACT (Sec ± SD)		
	Before Heparin	After Protamine	N
May 1982	138 ± 14	134 ± 12	51
May 1983	133 ± 19	133 ± 14	48
May 1984	137 ± 16	126 ± 16*	46
May 1985	146 ± 17	138 ± 14*	50
May 1986	150 ± 18	149 ± 16	42
May 1987	158 ± 21	144 ± 25*	33
May 1988	155 ± 20	146 ± 25*	36

ACT (Hemochron) values obtained from clinical records for the month of May of represented years. Comparison of preheparin and post-protamine statistical analysis by paired t test. Significance at $p < 0.05$*.

Table 2. Study Data

		ACT (Sec ± SD)		
		(P = Pediatric; A = Adult)		
		N	Before Heparin	After Protamine
1976 (4)	(P)	16	99 ± 6	99 ± 12
1987 (5)	(P)	22	125 ± 14	122 ± 18
1980 (6)	(A)	50	110 ± 13	113 ± 13

ACT (Hemochron) values obtained from our clinical investigations using consistent controlled methodology. No patients received prestudy anticoagulants. No significance ($p < 0.05$) between preheparin and post-protamine values by paired t test.

and may reflect the frequency of heparin therapy in our increasing population of patients with unstable angina for coronary artery surgery. Protamine is not a procoagulant and we are unaware of any study demonstrating improved coagulation following cardiopulmonary bypass.

The convenience of the automated ACT is largely responsible for its widespread use; however, bringing the laboratory to the bedside has its problems. Provision of equipment and materials with integrated quality controls for convenience and reliability is necessary. Regular control and testing of reagent and a tube containing a standard with which to verify machine function are needed to permit predictability. Even the limited precision and accuracy may be easily lost by the manner in which the automated ACT is most often utilized. Operator attention to detail including standardized agitation and consistent temperature of components as well as adherence to established procedure is mandatory to obtain meaningful results. Reproducible ACT values may be obtained (Table 2) only when consistent, controlled methodology, including exclusion of preoperative anticoagulant therapy, are employed.

The lowest safe limit of heparin effect may never be known. A prospective study in man whose endpoint is the demonstrable initiation of coagulation is unjustified on a risk/benefit basis. Instead, reliably demonstrated absence of the event is accepted as a guide. This may be reached by any of a number of methods and observations of which the ACT is only one and the value of 400 sec a prudent, but not necessarily precise lower limit. It will be less precise and less prudent if values are obtained by poor methodology.

David R. Jobes, MD
Norig Ellison, MD
Frederick W. Campbell, MD
Department of Anesthesia
University of Pennsylvania
Dulles Seven
3400 Spruce St.
Philadelphia, PA 19104

References

1. Gravlee GP, Case LD, Angert KC, Rogers AT, Miller GS. Variability of the activated coagulation time. Anesth Analg, 1988;67:469–472.
2. Young JA, Kisker CT, Doty DB. Adequate anticoagulation during cardiopulmonary bypass determined by activated clotting time and appearance of fibrin monomer. Ann Thoracic Surgery, 1978;26:231–240.
3. Personal Communication. International Technidyne Corporation, Edison, New Jersey.
4. Jobes DR, Bikhazi G, Ellison N. Rapid assessment of heparin anticoagulation and reversal. Abstracts of Scientific Papers, American Society of Anesthesiologists Annual Meeting, 1976, p. 437.
5. Jobes DR. Unpublished data.
6. Jobes DR, Schwartz AJ, Ellison N, Andrews R, Ruffini RA, Ruffini JJ. Monitoring heparin anticoagulation and its neutralization. Annals of Thoracic Surgery, 1981;31:161–166.

In Response:

Thank you for the opportunity to respond to the informative letter of Jobes, Campbell, and Ellison (1). I respect their expertise in activated coagulation time (ACT) technique and find their comments generally harmonious with the clinical report I co-authored (2). I second their plea for standardization of ACT technique and for a bloodless solution or tube that would permit standardization of Hemochron (International Technidyne Corp., Edison, NJ) devices. A mechanism using lyophilized bovine plasma is undergoing evaluation (3). Recently GA Harrison* and I used five Hemochron machines to perform 10 simultaneous saline clotting times on non-anticoagulated cardiac surgical patients using standardized technique. One machine produced significantly lower clotting times. In fairness to the manufacturer, these machines had not undergone internal calibration procedures for several years. This procedure can be performed by local biomedical engineering services and is recommended at least annually (3).

I believe that the ACT technique used in our report was well standardized, as judged by control and post-protamine ACT standard deviations comparable to those of Jobes et al. (1). We could not achieve their best coefficient of variation (CV) range (1.2–2.2%) probably because we did not pre-warm the ACT tubes. I think that most centers would find tube pre-warming impractical, and the CV values we reported for ACT-control (3.9 ± 5.0%) and ACT-protamine (3.1 ± 2.7%) using room-temperature tubes are clinically acceptable (2). We reported increased ACT variability during anticoagulation for cardiopulmonary bypass (CPB) not so much to advocate better precision (though this would be desirable) as to caution clinicians against unrealistic expectations when using ACTs to select heparin or protamine doses.

Jobes et al. (1) noted our incidental finding that ACT-control usually exceeded ACT-protamine, a finding they attribute to a heparin effect upon ACT-control in some

Table 1. Coagulation Tests in 21 Cardiac Surgical Patients

	Mean ± SD	Range
Preoperative APTT	25.3 ± 2.2	21.9–30.4
Postoperative APTT	33.1 ± 5.9*	24.6–45.0
Preoperative ACT	141 ± 16	111–175
Postoperative ACT	125 ± 14†	90–156

All numerical values expressed in seconds.
*$P \leq 0.0001$, compared with preoperative APTT (paired 2-tailed t-test).
†$P \leq 0.000$, compared with preoperative ACT (paired 2-tailed t-test).

patients. I must differ with their explanation. Although I agree that preoperative heparin use has increased and acknowledge that its effects can accumulate and linger, our report failed to note that the patients studied could have received only intravenous heparin preoperatively, usually as a continuous infusion. The 12-hour discontinuation period represents slightly more than six half-lives for heparin-induced clotting time prolongation from intravenous bolus doses below 200 IU/kg (4). The longest individual half-life reported under those conditions was 214 minutes (4). With rare exception, one would expect ACT prolongation from preoperative heparin to have fully dissipated by the time the ACT-control samples were taken. Further, we have reproduced post-protamine ACT reduction in a group of 21 cardiac surgical patients who received no preoperative heparin (Table). Activated partial thromboplastin times (APTTs) are also reported because that test is more sensitive to heparin-induced prolongation than the ACT (5). Postoperative APTT and ACT samples were collected 5 minutes after completing protamine infusion, at which time each patient had undetectable blood heparin concentrations by automated protamine titration (HemoTec Inc., Englewood, CO). Preoperative ACT exceeded post-protamine ACT in 17 of 21 patients, while preoperative APTT exceeded post-protamine APTT in just 1 patient. The opposite directional trends in ACT and APTT are confusing but genuine, and do not require a heparin effect.

If not because of heparin, why might preoperative ACT exceed post-protamine ACT? Using plasma fibrinopeptide A levels as a marker of plasma coagulation activity, surgery activates the coagulation cascade (6). This might decrease ACT or APTT below their preoperative values. If so, why wouldn't APTT show the same post-protamine trend as ACT? APTT is probably more sensitive than ACT to CPB-induced dilution of plasma coagulation factors. Small post-CPB APTT increases might also reflect unneutralized plasma heparin concentrations below the detection threshold for ACT or automated protamine titration; or protamine excess below the sensitivity of ACT.

Glenn P. Gravlee, MD
Department of Anesthesiology
Bowman Gray School of Medicine of
Wake Forest University
Winston-Salem, NC 27103

References

1. Jobes DR, Campbell FW, Ellison N. Limit(ation)s for ACT. Anesth Analg 1989;69:1008–9.
2. Gravlee GP, Case LD, Angert KC, Rogers AT, Miller GS. Variability of the activated coagulation time. Anesth Analg 1988;67:469–72.
3. Brady T. Personal communication (International Technidyne Corp., Edison, NJ).
4. Estes JW. Clinical pharmacokinetics of heparin. Clin Pharmacokinet 1980;5:204–20.
5. Congdon JE, Kardinal CG, Wallin JD. Monitoring heparin therapy in hemodialysis. JAMA 1973;227:1529–33.
6. Haddon WS, Gravlee GP, Bean VE, Miller GS, Angert KC. The activated coagulation time independently determines adequate anticoagulation during hypothermic cardiopulmonary bypass. Anesthesiology 1987;67:A26.

Book Reviews

General Anaesthesia 5th Edition

Edited by J. F. Nunn, J. E. Utting, and B. R. Brown, Jr,
Boston, Butterworths, 1989, 1434 pp, $150.00.

With the retirement of Cecil Gray, the fifth edition of *General Anaesthesia* has taken on a more international flavor, with Burnell Brown joining the editorial team. Although the 132 authors are from nine countries, principally the U.K. and the U.S.A., the British impact extends beyond the extra "a" in the title—e.g., the advice in the obstetrics chapter to "have the surgeon and 'sister' unscrub and help" requires a second reading by most readers residing west of the Atlantic. Fortunately the book retains its title for historical reasons only and covers all aspects of anesthesia, including regional, ICU, and pain clinic. Large volumes such as this are used primarily as a reference, and this reviewer used the 42 sets of questions prepared for the 1989 Spring Oral Boards as the basis for his review, checking each question against the index and table of contents.

On the basis of that review, the book is an excellent reference with a particularly fine index (although "intestinal obstruction" was not cited despite the specific section in the chapter on abdominal surgery). The frequent references to other chapters reflect tight editing of the individually authored chapters, but the organization of the chapters into eleven sections ranging from "Fundamentals of Anesthesia" through "Preop Period" to "Postop Period" and "Medicolegal" does create confusion. Information on renal aspects of anesthesia must be sought in chapters on "Effects of Anesthesia and Surgery on Renal Function" ("Fundamentals Section"), "Pre-existing Renal Disease" ("Preop Period"), and/or "Anesthesia for Patients with Renal Disease" ("Special Problems"). This repetition is both a strength and weakness, permitting several authorities to address a subject from a different perspective. For example, the risk of prior myocardial infarction in the anesthetized patient is alluded to in the chapter on vascular surgery, discussed in the chapter on patients with dysfunction of the circulatory system, and dissected in the chapter on preoperative assessment.

Chapters even in the same section vary greatly, with some—such as the obstetrics chapters—providing sound physiologic basis for the recommendations that follow for specific conditions and others, such as the chapter on neonatal anesthesia, being confined strictly to reviewing the physiologic basis for general recommendations, without mention of specific conditions. The only statements found with which this reviewer would take exception were the flat statement re "recurization" in the chapter on "Postoperative Recovery" and the endorsement of microaggregate filters when administering whole blood in the chapter on "Trauma and Surgery."

In summary, the fifth edition of *General Anaesthesia* continues the tradition of excellence, although the book has not quite achieved the international flavor referred to in the preface. Clearly the text belongs in every anesthesia department library but may be too dear at the list price for all anesthesiologists to buy.

Norig Ellison, MD
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Clinical Anesthesia

Edited by Paul G. Barash, Bruce F. Cullen, and Robert K. Stoelting, Philadelphia, J. B. Lippincott, 1989, 1575 pp, $95.00.

This 7-pound, 55-chapter newly arrived text is the latest addition to the ever-expanding library of anesthesia textbooks. Webster's Dictionary defines a textbook as "a book used in the study of a subject, one containing work relevant to the study of a subject." Whether this new textbook contains all that is relevant to anesthesiologists and nothing that is not is a matter of judgment. The acid test of a good textbook, in my opinion, is the ease and frequency with which we find answers to our questions, without having to resort to subspecialty books. If my test is valid, then *Clinical Anesthesia* is a textbook par excellence.

The 86 contributors cover the basic and clinical sciences of anesthesia as well as critical care and pain management. Most chapters are as thorough and complete as is reasonably possible, and the book can be carried around without dislocating a shoulder.

The majority of chapters include the most recent developments in our specialty. The chapter on history of anesthesia includes a paragraph on "Women in Anesthesia" (and one on "Anesthesia in Canada," for reasons not clear); the chapter on legal aspects of anesthesia includes the complete ASA "Standards for Basic Intra-Operative Moni-

©1989 by the International Anesthesia Research Society

toring" and a guide on "What to Do When Sued" (this will probably become a popular Board question); the chapter on operating room hazards includes paragraphs on impairment, stress, and suicide among anesthesiologists; the chapter on "Research Design and Statistics" provides tips on how to read critically scientific reports.

Is there room for improvement? I believe there is. The editors, wisely, refrained from contributing chapters to the book and concentrated on editing. However, there is a lack of uniformity in structure and style among the chapters. Uniformity would help the reader find specific information when searching through the various chapters.

The chapter on physics would probably intimidate the bravest of the clinical anesthesiologists. Among its 94 equations you can find the one on "resonant angular frequency," and among its 44 figures, the one on the "fluorescence quenching phenomenon." If you did not know what gases are "compressible fluids," you may never find the section on the common gas laws.

Neither the chapter on muscle relaxants nor the one on monitoring provides sufficient information on elementary neuromuscular transmission monitoring. The chapter on muscle relaxants incorrectly describes the correlation between train-of-four and single twitch depression. The return of the 1st, 2nd, or 3rd response of train-of-four correlates with 90%, 80%, or 75% of single twitch depression respectively.

A few minor typographical errors are scattered about; certainly Lippincott's word processors can weed them out before the next edition appears. The body mass index is the ratio of the body weight, (kg)/height^2 in meters and not as stated on page 434. Chapter 25, entitled "Acid Base, Blood Gas, Electrolytes," contains no significant discussion of electrolytes. Electrolytes are discussed in chapter 27.

Since massive blood loss regularly occurs in the operating room, the reader could benefit from an algorithm on blood component replacement during massive transfusion. Particularly useful would be a guideline on when and in what proportions should the various components of blood as well as sodium bicarbonate and calcium (if at all) be administered. The chapter on "Nutrition, Fluid, and Electrolytes" does not mention the recent evidence that the composition of nutrition affects the patient's response to various drugs in general and to anesthetic drugs in particular.

The authors of the chapter on "Anesthesia for Genitourinary Surgery" quote an obsolete concept from a 1957 publication on the cause of a coagulopathy in transurethral prostatectomy patients. More recent studies clearly show that the common cause is disseminated intravascular coagulation accompanied by a secondary fibrinolysis (Friedman et al.: Arch Intern Med 124:341, 1969).

In the preface to the book, the editors state that their goal was "to create such a comprehensive usable book in a single volume." This they have accomplished. The book will be cherished by all members of the anesthesia team, whether they are in training or already accomplished anesthesiologists and anesthetists.

Isaac Azar, MD
Department of Anesthesiology
Beth Israel Medical Center
New York, New York

Effective Hemostasis in Cardiac Surgery

N. Ellison and D. R. Jobes, eds. Philadelphia: W. B. Saunders, 1988, 209 pp, $75.00.

This monograph was derived in part, from sessions held during the 1987 annual meeting of the Society of Cardiovascular Anesthesiologists and as such it represents the second in an annual series of similarly produced monographs. Although diminutive by comparison with many of our more standard text books, it is brim full of clearly written, current, "state of the art" discussion of hemostasis in cardiac surgery.

The text is comprehensive in its treatment of the topic and the individual chapters are virtually freestanding, in-depth, discussions of each subtopic. Despite this, the book flows well together and leads in a logical progression to the closing chapter which, in turn, neatly synthesizes the elements into a cohesive approach to the basic clinical problem—how to deal effectively with hemostatic problems in the cardiac surgical patient. Standout chapters are identified only with difficulty because the quality is uniformly high. However, Dr. Jan C. Harrow's discussion of protamine is one of the best concise reviews of the topic that I have seen to date. The chapter includes a very well-done historical perspective on protamine and provides a current presentation of the pathophysiology underlying adverse responses to protamine. Drs. Marengo-Rowe and Leveson, in what some would consider a controversial approach, present a strong case for the occurrence of accelerated fibrinolysis as a cause of excessive bleeding after cardiopulmonary bypass. They argue cogently for the use of antifibrinolytic agents in the treatment of that condition. The opposite end of the coagulation spectrum is well discussed by Drs. Judith A. Fabian and Lauraine Stewart in their consideration of fibrinolytic therapy and its implications for the patient who becomes an operative candidate. The discussion of platelet function by Drs. Campbell and Addonizio is an excellent synopsis of the current state of knowledge of platelet physiology and of the interactions between platelets and the apparatus necessary for cardiopulmonary bypass. This chapter is nicely complemented by the discussion of desmopressin acetate and its use after cardiopulmonary bypass written by Dr. J. Anthony Ware. Two chapters discuss the viscoelastic properties of clot formation and dissolution and also describe associated instrumentation (the thromboelastograph and the Sonoclot) while nicely presenting the more recent advances in the use of these instruments to diagnose, at least qualitatively, the hemostatic abnormalities associated with cardiac surgery.

The book is well published and well edited. There is abundant use of appropriate illustrations to clarify the authors' concepts. In short, this is a quality production and definitely deserves the attention of those of us involved in perioperative care of cardiac surgical patients.

Richard F. Davis, MD
Department of Anesthesiology
Portland Vererans Administration Medical Center
Portland, Ore

Illustrated Manual of Regional Anesthesia

P. Raj, H. Nolte, and M. Stanton-Hicks. Berlin: Springer-Verlag, 1988, 396 pp, $585.00.

At first impression the design of this monumental book is imaginative and innovative. The use of numerous transparencies to demonstrate the anatomy and the approaches for various regional anesthetic techniques makes it extremely useful for teaching purposes.

Unfortunately, there are also drawbacks with the approach used by the authors. This illustrated manual of regional anesthesia probably should not be considered as a single book in the classical sense but rather as two separate educational tools. The soft-covered manual could stand alone as a brief description of regional anesthetic techniques. However, if one considers the manual by itself it has certain advantages and disadvantages. The primary advantage is that the various techniques are simply presented with sufficient illustrations that the manual could be used as an aid in the performance of regional anesthetic techniques in an operating room environment. However, in the manual's current form, it duplicates many of the other technique books that have been published such as the classical books by Bonica or Moore and more recent publications including that by one of the authors, Dr. Raj.

This manual does reflect the excellent clinical skills of the three authors. Chapter 1 on principles of management is probably the weakest chapter, particularly with regard to the section on the basic principles of action of local anesthetic drugs. The remaining chapters that describe the various blocks following an anatomical classification are basically well presented.

Clearly it is the second portion of this book that distinguishes this work from other textbooks of regional anesthesia. The loose-leaf binder containing an incredible number of transparencies is what makes this innovative and imaginative. The removable plates that illustrate the techniques for almost every regional anesthetic procedure provide an excellent opportunity to teach not only the anatomy involved in regional anesthesia but also the approach that is necessary to block specific nerve entities.

A potential disadvantage is the fact that the transparencies can be lost or misplaced. It is not clear whether the publishers will offer a program for replacing lost transparencies. In addition, the major drawback to this work involves the cost of the manual. This probably is one of the most expensive works in anesthesia.

Thus, this is probably not a manual that will be widely purchased by individual practioners. However, it is clearly a manual that probably belongs in every teaching department of anesthesia since it does provide an excellent means of demonstrating all of the regional anesthetic techniques to residents and staff who are not experts in the practice of regional anesthesia.

In summary, although there may be drawbacks to this manual, the authors are certainly to be congratulated for the enormous efforts that were required to develop this innovative manual of regional anesthesia.

Aaron J. Gissen, MD
Department of Anesthesia
Harvard Medical School
Boston, Mass

Erratum

In "The Effect of Epidural Sufentanil on Shivering and Body Temperature in the Parturient," published in the April issue, pages 530–3, two measurements are misstated. Page 530, column 2, line 34 should read "0.2 mg of epinephrine," and on page 531, line 3 of the caption for Figure 1 should—again—read "0.2 mg."

- An exciting journal for the dissemination of clinical and basic science research relating to acute care medicine and resuscitation -

Resuscitation

Editor-in-Chief
John B. McCabe M.D., F.A.C.E.P.
SUNY - Health Science Center - Syracuse, Dept. of Critical Care and Emergency Medicine, 750 E. Adams Street, Syracuse, New York 13210, U.S.A.

Special features of *Resuscitation*:

- ***The only journal*** in the area of resuscitation that is general in nature and not specific to a single body system
- Good balance between basic research and clinical publications
- Good outlet for publishing new and innovative animal models for human resuscitation problems
- Includes information of interest to the critical care practitioner, emergency medicine practitioner, anesthesiologist, neurologist, cardiologist and laboratory investigator.

Aims and Scope

Resuscitation is a bimonthly, international, interdisciplinary medical journal. The papers published deal with the etiology, pathophysiology, diagnosis and treatment of acute diseases. Clinical and experimental research, reviews and case histories used in clinical resuscitation or experimental resuscitation research are encouraged.

Editorial Policy

The originality of content of papers submitted and the quality of the work on which they are based is the prime consideration of the editors. The decision of the Editor-in-Chief advised by reviewers is final.

Editorial Board

Friedrich W. Ahnefeld *(Ulm)*
Dario Birolini *(Sao Paulo)*
Charles Brown *(Columbus, OH)*
Simon Bursztein *(Haifa)*
Hao-Hui Chen *(Beijing)*
Herman H. Delooz *(Leuven)*
Ruth V.W. Dimlich *(Cincinnati, OH)*
Alan G. Gilston *(London)*
Maurice Goulon *(Paris)*
Tsuguharu Ishida *(Hyogo)*
Michael S. Jastremski *(Syracuse, NY)*
Karl Kern *(Tucson, AZ)*
Gary Krause *(Detroit, MI)*
Keith Little *(Edinburgh)*
Armand Lowenthal *(Antwerp)*
Nobuo Nishimura *(Tokyo)*
Murray M. Pollack *(Washington, DC)*
Harlan Stueven *(Milwaukee, WI)*
Per Vaagenes *(Oslo)*
W.D. Voorhees III
David Zideman *(London)*

Consulting Editors

Vladimir A. Negovsky *(Moscow)*
Peter Safar *(Pittsburgh, PA)*

Cited/abstracted in: Chemical Abstracts; Current Contents; Excerpta Medica (EMBASE); Index Medicus (MEDLINE); PASCAL M

Subscription Information 1989:
Volumes 17 and 18 (2 vols. in 6 issues)
Subscription rate: US $282.00
Personal rate: US $65.00
(prices include postage and handling)
ISSN 0300-9572

ELSEVIER
Send your orders to:
Elsevier Scientific Publishers Ireland, Ltd., P.O. Box 85, Limerick, Ireland.
Requests for FREE SAMPLE COPIES should be sent to:

In the USA and Canada:
Journal Information Center,
Elsevier Science Publishers,
P.O. Box 882, Madison Square Station,
New York, NY 10159, U.S.A.

In all other countries:
Elsevier Scientific Publishers Ireland Ltd.,
P.O. Box 85,
Limerick,
Ireland.

The US$ price is definitive

ISSN 0003-2999
Volume 69, Number 2, August 1989

Anesthesia and Analgesia

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

Anesthesia and Analgesia

Journal of International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-1130

Editorial Board

Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada
Phillip O. Bridenbaugh, MD, Cincinnati, Ohio
Mieczyslaw Finster, MD, New York, New York
Thomas J. Gal, MD, Charlottesville, Virginia
Paul R. Hickey, MD, Boston, Massachusetts
Edward D. Miller, Jr, MD, New York, New York
Walter S. Nimmo, MD, BSC, FRCP, FFARCS, Sheffield, United Kingdom
Nathan L. Pace, MD, Salt Lake City, Utah
Richard J. Palahniuk, MD, Minneapolis, Minnesota
Ronald G. Pearl, MD, PhD, Stanford, California
Donald S. Prough, MD, Winston-Salem, North Carolina
Joseph G. Reves, MD, Durham, North Carolina
John J. Savarese, MD, New York, New York
John H. Tinker, MD, Iowa City, Iowa
Barbara E. Waud, MD, Worcester, Massachusetts

Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 655 Avenue of the Americas, New York, NY 10010, prices on request.

This journal is printed on acid free paper.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Martin, MD, Edward D. Miller, Jr, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K. C. Wong, MD, PhD. Emeritus Trustees are: Paul R. Dumke, MD, Morris J. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1989 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1989 applying to IARS members: USA and possessions, $70.00 per year, in all other countries $89.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited by anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

Subscription information for 1989 applying to non-IARS members: Institutions, $112.00; nonmember individuals, $85.00. Outside of the USA and possessions, please add $19.00 for surface postage and handling. For airmail, add $65.00 in USA, Canada, and Mexico, $46.00 for surface airlift to Europe, $65.00 for surface airlift to Japan, and $130.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical science, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views and recommendations as to medical procedures, choice of drugs and drug dosages are the responsibility of the authors.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

CALCU

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1990 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1990 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **January 15, 1990.** Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1990 Award(s) will be announced at the Annual Scientific Meeting (64th Congress) of the International Anesthesia Research Society to be held at the Sheraton-Waikiki Hotel. Honolulu, Hawaii, March 9-13, 1990.

Anesthesia and Analgesia

Volume 69 Number 2, August 1989

Contents

EDITORIAL

Carbon Dioxide and Hepatic Circulation *Simon Gelman* 149

SCIENTIFIC ARTICLES

Effects of Hypocapnia and Hypercapnia on Splanchnic Circulation and Hepatic Function in the Beagle *Yoshihisa Fujita, Takayuki Sakai, Akiyuki Ohsumi, and Masuhiko Takaori* 152

Effects of Succinylcholine at the Masseter and Adductor Pollicis Muscles in Adults *Charles E. Smith, Francois Donati, and David R. Bevan* 158

Alterations in Host Defense Associated with Inhalation Anesthesia and Blood Transfusion *J. Paul Waymack, Phillip Miskell, and Sara Gonce* 163

A Comparison of EEG Determinants of Near-Awakening from Isoflurance and Fentanyl Anesthesia: Spectral Edge, Median Power Frequency, and δ Ratio *Charles W. Long, Nitin K. Shah, Christopher Loughlin, John Spydell, and Robert F. Bedford* 169

Normovolemic Hemodilution and Lumbar Epidural Anesthesia *Stéphane Mouren, Jean-François Baron, Bertrand Hag, Martine Arthaud, and Pierre Viars* 174

Tachyphylaxis Associated with Repeated Epidural Injections of Lidocaine Is Not Related to Changes in Distribution or the Rate of Elimination from the Epidural Space *Torben Mogensen, Lene Simonsen, Nicholas B. Scott, Jens H. Henriksen, and Henrik Kehlet* 180

Intrathecal Clonidine Suppresses Noxiously Evoked Activity of Spinal Wide Dynamic Range Neurons in Cats *Kenji Murata, Itsuo Nakagawa, Yukihiro Kumeta, Luke M. Kitahata, and J. G. Collins* 185

Intraoperative Temperature Monitoring Sites in Infants and Children and the Effect of Inspired Gas Warming on Esophageal Temperature *Bruno Bissonnette, Daniel I. Sessler, and Pierre LaFlamme* 192

Pituitary-Adrenal Stress Response in the Absence of Brain-Pituitary Connections *Daniel B. Carr, Jane C. Ballantyne, Patricia F. Osgood, James W. Kemp, and Stanislaw K. Szyfelbein* 197

Esmolol for Potentiation of Nitroprusside-Induced Hypotension: Impact on the Cardiovascular, Adrenergic, and Renin-Angiotensin Systems in Man *Richard Edmondson, Oscar Del Valle, Nitin Shah, George Wong, Donna Dwyer, Deborah Matarazzo, Alisa Thorne, Charles Coffey, and Robert Bedford* 202

Early Postoperative Arterial Oxygen Desaturation: Determining Factors and Response to Oxygen Therapy *Jaume Canet, Montserrat Ricos, and Fernando Vidal* 207

NOW PUBLISHED BY ELSEVIER

Editor

Raymond A. Dionne, DDS, PhD, National Institute of Dental Research,
Bethesda, MD

Anesthesia Progress

A Journal for Pain and Anxiety Control

Editorial Review Panel
Glenn Clark, DDS, MS, University of California, Los Angeles
Stephen Cooper, DMD, PhD, University of Pennsylvania
Paul Desjardins, DMD, PhD, University of Medicine and Dentistry of New Jersey
Tommy Gage, DDS, PhD, Baylor University, Texas
John Gregg, DDS, PhD, Blacksburg, Virginia
Milton Houpt, DDS, PhD, University of Medicine and Dentistry of New Jersey
Barbara Melamed, PhD, University of Florida
Paul Moore, DMD, PhD, University of Pittsburgh, Pennsylvania
Michael Roizen, MD, University of Chicago
Allen Sisk, DDS, Medical College of Georgia
John Yagiela, DDS, PhD, University of California, Los Angeles

Editorial Consultant
Henry M. Koehler

Anesthesia Progress, the premier journal devoted to the management of patient pain and anxiety in dentistry, is now published by Elsevier. Established over 30 years ago, **Anesthesia Progress** is a highly respected, peer-reviewed journal reporting current information for professionals in the field of anesthesia and pain control.

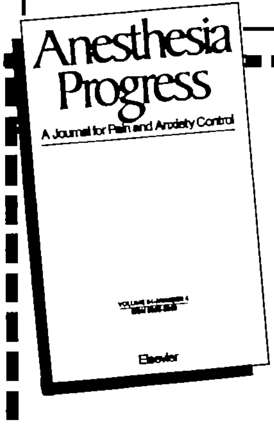
Anesthesia Progress, the official journal of the American Dental Society of Anesthesiology, features clinical and research articles, review articles, case reports, literature reviews, meeting updates, letters to the editor, and a Continuing Education Calendar. The journal's rigorous peer review process ensures the reader a wealth of scientifically valid, practical information on the safe and effective treatment of patient pain and anxiety.

In order to provide the widest possible coverage of the field, **Anesthesia Progress** reports on all of the following topics:

- **general anesthesia**
- **conscious sedation**
- **local anesthesia**
- **analgesics**
- **IV sedation**
- **chronic pain**
- **pediatric sedation**
- **behavioral methods of anxiety control**
- **drug-induced emergencies**
- **education in pain and anxiety control**
- **evaluation of new and standard drugs**

Anesthesia Progress is abstracted/indexed in *Biological Abstracts* (BIOSIS), *Excerpta Medica* (EMBASE), *Index to Dental Literature* (MEDLINE), *Periodicals Digest in Dentistry.*

1989 Subscription Information
Volume 36 (6 issues), 1989. ISSN 0003-3006
Institutional rate: $60.00. Personal rate: $38.00



ORDER FORM

Anesthesia Progress ISSN 0003-3006
Volume 36 (6 issues) 1989
Please enter my 1989 subscription at the following rate:
☐ Institutional: $60.00 ☐ Personal: $38.00
(Note: Please add $21.00 for postage and handling outside the U.S.)
☐ Please send me a free sample copy.

Payment
Enclosed is my:
☐ personal check ☐ bank draft
Please charge to:
☐ American Express ☐ VISA
☐ MasterCard (issuing bank #____________)
Account #____________ Expires ________
Signature ____________

☐ **Please bill me.** (Personal subscriptions must be prepaid by check or charge card. Orders from non-U.S. customers must be prepaid.)

Name ____________
Address ____________
City ____________
State ________ Zip/Postal Code ________

For sample copies send to:
in North America:
Elsevier Science Publishing Co., Inc.
P.O. Box 882, Madison Square Station
New York, NY 10159
in the rest of the world:
Elsevier Science Publishers, Direct Mail Department, P.O. Box 211, 1000 AE Amsterdam, The Netherlands

Note: Send subscription orders to the New York address. Subscription rates valid until December 31, 1989. Please allow 6-8 weeks for delivery of the first issue.

10/88 V9AF BILL828A

Midazolam-Alfentanil Synergism for Anesthetic Induction in Patients *H. R. Vinik, E. L. Bradley jr, and I. Kissin* 213

Solubility of I-653, Sevoflurane, Isoflurane, and Halothane in Plastics and Rubber Composing a Conventional Anesthetic Circuit *Alexander G. Targ, Nobuhiko Yasuda, and Edmond I. Eger II* 218

Ether Does Not Antagonize Bronchoconstriction Caused by Acetylcholine, Histamine, or Phenylephrine *Paul Neill and James W. Sleigh* 226

REVIEW ARTICLE

Noninvasive Transcutaneous Cardiac Pacing *Jeffrey S. Kelly and Roger L. Royster* 229

CLINICAL REPORTS

Autotransfusor Removal of Fentanyl from Blood *Leland H. Hanowell, John H. Eisele jr, and Evangeline V. Erskine* 239

Ulnar Train-of-Four Stimulation in Predicting Face Movement during Intracranial Facial Nerve Stimulation *Larry C. Ho, Gregory Crosby, Pennathur Sundaram, Steven F. Ronner, and Robert G. Ojemann* 242

Metabolism of Isoflurane in Patients Receiving Isoniazid *Ian S. Gauntlett, Donald D. Koblin, Mark R. Fahey, Krystyna Konopka, Larry D. Gruenke, Lucy Waskell, and Edmond I. Eger II* 245

Intravenous Injection of Liquid Halothane *R. Dwyer and D. L. Coppel* 250

Etomidate Myoclonus and the Open Globe *James M. Berry and Robert G. Merin* 256

LETTERS TO THE EDITOR

"Sciatic Radicular Pain" or Piriformis Muscle Syndrome? *Zia Durrani* 260

Pseudosciatica *Gary Arthur Ogin* 261

Sciatica and the Cerebrospinal Fluid *Leroy D. Vandam* 261

Blockade of Sciatic Nerve Branches Relieves Sciatic Radicular Pain *Igor Kissin, Anne V. Xavier, and Judy McDanal* 262

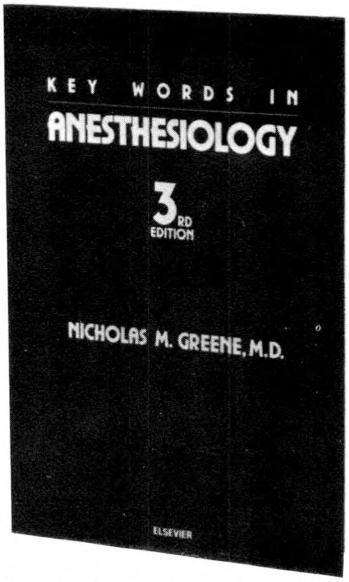
"Statistical Power" and Interpretation of Small Studies: Does Atracurium Pretreatment Reduce the Incidence of Succinylcholine Fasciculations? *Paul Burton, Jennifer Kurinczuk, and Eric De Melo* 263

Venous Air Embolism during Hip Arthrography *Richard G. Hetherington and Patrick M. McQuillan* 264

Cimetidine in Anaphylactic Shock Refractory to Standard Therapy *Hernando De Soto and Paul Turk* 264

The Effect of Fingerprinting Ink on Pulse Oximetry *Michael F. Battito* 265

New from Elsevier



KEY WORDS IN
ANESTHESIOLOGY
3RD EDITION
NICHOLAS M. GREENE, M.D.
ELSEVIER

KEY WORDS IN ANESTHESIOLOGY,

3rd Edition

By **NICHOLAS M. GREENE,** MD, Professor, Department of Anesthesiology,
Yale University School of Medicine

This unique booklet presents an updated list of significant words with appropriate subheadings and cross-references that allow anesthesiologists as well as reference librarians to better organize their filing systems. As a well-recognized editor in the field of anesthesiology, Dr. Greene is singularly qualified to write this book.

Key Words in Anesthesiology:

- provides entry points into information retrieval systems
- supplies a base for the standardization of terminology used in anesthesiology
- provides a framework that allows for the orderly and systematic study of anesthesiology

Dr. Greene is currently editor-in-chief of **Anesthesia and Analgesia,** and is the former editor of the journal **Anesthesiology.** He was responsible for the introduction and execution of this key word system in both publications.

Key Words in Anesthesiology is an important tool for anyone interested in anesthesiology.

1988 65 pages paper 0-444-01320-2 $10.00

ORDER FORM

Please send me ______ copy(ies) of **Key Words in Anesthesiology,** by Greene, 0-444-01320-2, $10.00.

☐ **Check enclosed** (NY State residents please add applicable sales tax.)

Charge my ☐ American Express ☐ VISA
☐ MasterCard ______________________
(issuing bank no.)
Account # ______________ Expiration Date ______
Signature ______________________

10/88 V8AD

Name ______________________
Address ______________________
City __________ State _____ Zip/Postal Code _____

Note: Book prices subject to change without notice.

Return to:

Elsevier Science Publishing Co. Inc.
P.O. Box 882, Madison Square Station
New York, NY 10159

Pulse Oximetry Probe Disconnection	*Dennis F. Landers, Myrna C. Newland, and Laurence Wolpert*	265
An Anesthetic Adapter for All Metered Dose Inhalers that Is Readily Available to All	*Adolph J. Koska III and David G. Bjoraker*	266
Inability to Thread Epidural Catheter through Epidural Needle	*David T. Seitman and Bryan E. Shapiro*	267
Aminophylline Reversal of Midazolam Sedation	*Jonathan S. Gallen*	268
Severe Lightning Pain after Spinal Anesthesia in a Patient with Tabes Dorsalis	*Daisuke Sugiyama, Katsuya Nobuhara, Nobuhiro Maekawa, and Hidefumi Obara*	268

BOOK REVIEWS

Cancer Pain	*Rudolph H. de Jong*	270
Anesthesia and the Heart Patient	*G. Bashein*	270
Clinical Anatomy for Anesthesiologists	*Duane K. Rorie*	271
Anatomy for Anaesthetists (fifth edition)	*Duane K. Rorie*	271

Historical Notes 244
259

References: 1. Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stress associated with worse outcome? *Anesthesiology.* 1987;67:A1. Abstract. **2.** Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. *Anesthesiology.* 1986;65:A516. Abstract. **3.** de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. *Anesthesiology.* 1982;56:112-118. **4.** Flacke JW, Bloor BC, Kripke BJ, et al: Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: A double-blind study. *Anesth Analg* 1985;64:897-910. **5.** Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. *Anesthesiology.* 1987;66:130-135.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

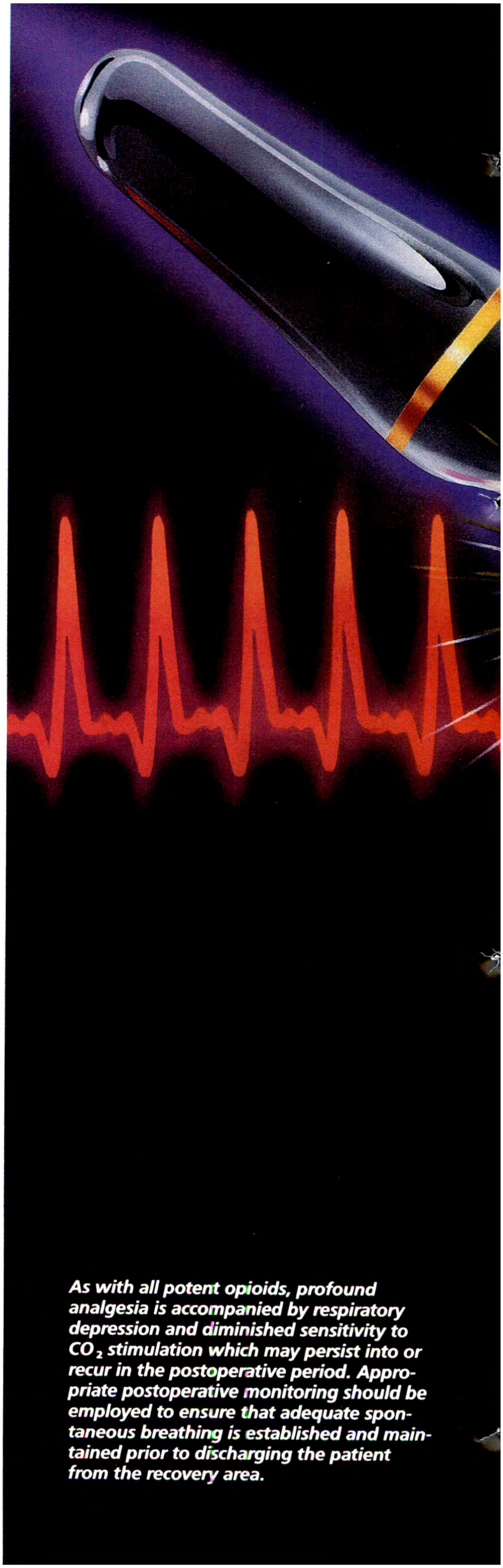
DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely.

Protect from light. Store at room temperature 15°-30° C (59°-86° F).

March 1986, March 1987
U.S Patent No. 3,998,834
7618505-M

JANSSEN
PHARMACEUTICA

Piscataway, NJ 08854 © Janssen Pharmaceutica Inc. 1989 JPI-SU-025



As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Editorial

Carbon Dioxide and Hepatic Circulation

Simon Gelman, MD, PhD

The study by Fujita and collaborators (1) examined the effect of hypo– and hypercarbia on hepatic circulation and function. The results of the study partially confirm but partially contradict some observations already available in the literature. For example, Fujita et al. (1) observed a decrease in hepatic arterial blood flow during hypocarbia while Gelman et al. (2) demonstrated an increase in hepatic arterial blood flow. Fujita et al. (1) observed a decrease in hepatic oxygen uptake during hypercarbia while Thomson et al. (3) observed an increase. The relevant question here is who is right and who is wrong? Who made a mistake during the experiments? The answers to such questions are not always easy. This editorial attempts to address these questions and to place the Fujita et al. (1) work in perspective.

In clinical settings, as well as in experimental laboratory environment while performing studies on the whole animal, we are dealing with an extremely complex combination of factors affecting one or another organ's function, including hepatic circulation and function. Such a combination consists of anesthesia *per se,* surgical stress opposed to different degrees by one or another type of anesthetic management, controlled ventilation with subsequent changes in intrathoracic pressure, as well as in gas exchange. Obviously, this combination includes changes in blood volume and functions of other organs and systems through which hepatic circulation and function might alter (4).

Anesthetics alter the splanchnic circulation by different mechanisms acting on the various factors controlling splanchnic blood flow. Systemic hemodynamics (cardiac output, blood volume, vascular resistance, blood pressure), neural and humoral mechanisms (including the release of stress hormones and mediators such as cortisol, catecholamines, antidiuretic hormone, etc.), and changes in oxygen requirements are the main factors, directly and indirectly affecting the splanchnic and hepatic circulation during anesthesia.

The mechanisms of hepatic circulatory disorders during surgery apparently involve tractions and manipulations on the viscera. However, the main role probably belongs to a general biological response to stress: laparotomy causes marked mesenteric vasoconstriction and a decrease in blood flow through gastrointestinal tract which can be completely abolished by hypophysectomy (5). Surgical stress is usually associated with a release of various hormones and substances, including catecholamines, renin-angiotension, vasopressin, etc., which can and do disturb the splanchnic circulation. The degree of splanchnic circulatory disturbances and the decrease in hepatic blood flow mainly depends on the type of surgical intervention: minor peripheral procedures are accompanied by a small degree of blood flow reduction while major procedures, such as laparotomy, are associated with a substantial decrease in hepatic blood flow (6). On the other hand, the degree of hepatic blood flow reduction during similar surgical stress might also depend on the choice of anesthetic: one anesthetic can reduce stress-induced splanchnic circulatory disturbances to a greater extent than another (6,7). The lesson is clear: surgical intervention rather than anesthesia is the main determinant of alterations in the splanchnic and hepatic circulation, and anesthesia can play a modifying role in circulatory disturbances developing during surgical stress.

Ventilation, spontaneous and especially con-

Supported by Grant 37611–02.

Received from the Department of Anesthesiology, The University of Alabama at Birmingham, School of Medicine, 619 South 19th Street, Birmingham, Alabama. Accepted for publication February 27, 1989.

Address correspondence to Dr. Gelman, Department of Anesthesiology, The University of Alabama at Birmingham, School of Medicine, 619 South 19th Street, Birmingham, AL 35233.

©1989 by the International Anesthesia Research Society

trolled, affects the hepatic circulation. During spontaneous inspiration, the diaphragm is displaced downward, compressing the liver. This results in an accumulation of blood behind the liver in the splanchnic vasculature and a decrease in total splanchnic outflow. At the same time, intrathoracic and caval vein pressures decrease. This facilitates inferior caval vein blood flow from the kidneys and lower extremities. Opposite effects occur during expiration when the diaphragm is displaced upward, releasing the compression of the liver, decreasing hepatic venous pressure, and thereby facilitating an increase in splanchnic outflow. At the same time, intrathoracic and caval vein pressures increase, diminishing the pressure gradient for venous return and venous outflow from the lower part of the body. Such an arrangement maintains the stability of venous return through the inferior caval vein, which predominately consists of blood flow from the lower part of the body during inspiration and from the splanchnic system during expiration (8).

It is obvious that controlled ventilation, with associated dramatic changes in intrathoracic and intraabdominal pressures, alters the elegant relationship between splanchnic venous outflow and venous outflow from the kidneys and lower extremities. During expiration, which is usually spontaneous during controlled ventilation, the relationship would be the same as during spontaneous ventilation. However, during controlled inspiration, the associated substantial increase in intrathoracic pressure causes the venous outflow from the splanchnic system to meet greater impedance than during spontaneous inspiration. There are data demonstrating that continuous positive pressure ventilation, especially with a large tidal volume or with an increased end-expiratory pressure, decreases splanchnic blood flow (9–11). Apparently, anesthesia can modify certain neurogenic mechanisms, compensating such effects. For example, in one study, controlled ventilation, compared with free breathing, had a tendency to reduce intestinal, splenic, and hepatic arterial blood flows during pentobarbital, but not during chloralose anesthesia (12).

The work by Fujita et al. (1) examined the effects of carbon dioxide, a rather important component of the combination (surgery, anesthesia, controlled ventilation) that we usually deal with in the operating rooms. The investigators provided the same surgical stress (laparotomy and blood flow measurements with electromagnetic flowmeters), as well as the same anesthesia, and the same parameters of controlled ventilation for each level of carbon dioxide studied. Hypo- and hypercarbia were achieved by changing the size of dead space.

Fujita et al. (1) demonstrated some tendencies for a decrease in portal blood flow (statistical significance was not achieved). Had they had a larger number of observations, they could have possibly found the difference. Therefore, their observations do not really contradict the data (13–15) demonstrating that hypocarbia decreases portal blood flow. On the other hand, they did note a decrease in hepatic arterial blood flow contrary to observations by others (2). Who is right? I think both groups are: Gelman et al. (2) performed their experiments on monkeys without laparotomy, examining the "pure" effect of hypocarbia while Fujita et al. (1) examined the effects of hypocarbia in combination with surgical stress (laparotomy). A decrease in portal blood flow by itself usually leads to an increase in hepatic arterial blood flow (16). Laparotomy per se is accompanied by a reduction in portal blood flow and an increase in hepatic arterial blood flow (6,17). Therefore, it is possible that hypocarbia applied after laparotomy decreased hepatic arterial blood flow from already increased levels. In fact, during normocarbia in Fujita et al. (1) observations, the arterial fraction of total hepatic blood flow was about 40% while in "normal" (without laparotomy) situations, the arterial fraction usually equals 25%–30% of total hepatic blood flow (18,19). Thus, there is really no contradiction between these data: hypocarbia per se probably increases hepatic arterial blood flow while hypocarbia and superimposed surgical stress might reduce it.

During hypercarbia, Fujita et al. (1) observed increases in portal and total hepatic blood flows which are most probably mediated through carbon dioxide directly induced vasodilation and an increase in cardiac output, resulting from stimulation of the sympathetic nervous system. These observations agree with other studies in the field. An increase in portal venous pressure observed by Fujita et al. (1) has also been observed by others (3) and apparently results from enhanced portal blood flow and/or increased intrahepatic portal venular resistance (20). A decrease in hepatic oxygen uptake combined with a decrease in indocyanine clearance (ICG) is an unexpected and somewhat puzzling observation. Others demonstrated an increase in hepatic oxygen uptake during hypercarbia which was attributed to an increase in sympathetic discharge (3). If Fujita et al. (1) observed only a decrease in ICG clearance, one could have challenged the results by saying that the investigators did not measure the changes in ICG concentrations in the hepatic venous blood and, since ICG is eliminated from the body not only by the liver (21,22), the results could have been inaccurate. However, hepatic oxygen uptake was determined by a technique completely independent from the ICG clearance method. The underlying mechanism for a decrease in hepatic oxygen uptake and ICG clearance might be mutual. These mechanisms might involve a decrease in intracellular pH with subsequent deterioration of cellular function. There is an alternative hypothetical mechanism: carbon dioxide is a well-known vasodilator in many tissues but not necessarily in the liver. For example, acidosis, either metabolic or respiratory, increases intrahepatic portal venular resistance (20) and, therefore, might increase shunting of the blood through the nonfunctioning vessels (possibly even dilated sinusoids) bypassing the hepatotocytes; this might result in insufficient delivery of oxygen and ICG to the hepatocytes. This particular observation, namely, that hypercarbia-induced increase in hepatic blood flow is associated with a decrease in hepatic oxygen uptake and clearance of ICG and possibly other substances, may have rather interesting implications for future research in the area as well as for our understanding of many events occurring in the operating rooms and intensive care units. Besides, this observation illustrates that high oxygen content in any venous blood might not necessarily imply adequate oxygenation and function of a tissue.

Thus, Fujita et al. (1) looked at one component, the role of carbon dioxide, in the combination of surgical stress, anesthesia, and controlled ventilation, on hepatic circulation and function. They demonstrated again that this combination is extremely complex. What are the possible clinical implications of this study? This and other observations suggest that moderate degrees of hypocarbia do not deteriorate hepatic circulation and function to a significant extent, while hypercarbia might cause temporary hepatic dysfunction. Future studies will verify these findings and determine the extent of the danger.

References

1. Fujita Y, Sakai T, Ohsumi A, Takaori M. Effects of hypocapnia and hypercapnia on splanchnic circulation and hepatic function in the beagle. Anesth Analg 1989 (in press).
2. Gelman S, Fowler KC, Bishop SP, Smith LR. Cardiac output distribution and regional blood flow during hypocarbia in monkeys. J Appl Physiol 1985;58:1225–30.
3. Thomson IA, Fitch W, Hughes RL, Campbell D. Effect of increased concentrations of carbon dioxide during halothane anaesthesia on liver blood flow and hepatic oxygen consumption. Br J Anaesth 1983;55:1231–7.
4. Gelman S. General anesthesia and hepatic circulation. Can J Physiol Pharmacol 1987;65:1762–79.
5. McNeill JR, Pang CC. Effect of pentobarbital anesthesia and surgery on the control of arterial pressure and mesenteric resistance in cats. Role of vasopressin and angiotensin. Can J Physiol Pharmacol 1982;60:363–8.
6. Gelman S. Disturbances in hepatic blood flow during anesthesia and surgery. Arch Surg 1976;111:881–3.
7. Gelman S, Dillard E, Bradley EL Jr. Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane, or fentanyl. Anesth Analg 1987;66:936–43.
8. Moreno AH, Burchell AR. Respiratory regulation of splanchnic and systemic venous return in normal subjects and in patients with hepatic cirrhosis. Surg Gynecol Obstet 1982;154:257–67.
9. Johnson EE. Splanchnic hemodynamic response to passive hyperventilation. J Appl Physiol 1975;38:156–62.
10. Manny J, Justice R, Hechtman HB. Abnormalities in organ blood flow and its distribution during positive end-expiratory pressure. Surgery 1979;85:425–32.
11. Halden E, Jakobson S, Janeras L, Norlen K. Effects of positive end-expiratory pressure on cardiac output distribution in the pig. Acta Anaesthesiol Scand 1982;26:403–8.
12. DeCastro MTBB, Downey HF, Crystal GJ, Bashour FA. Effect of controlled ventilation on renal and splanchnic blood flows during nicotine. Am J Physiol 1985;248:H360–H5.
13. Hughes RL, Mathie RT, Fitch W, Campbell D. Liver blood flow and oxygen consumption during hypocapnia and IPPV in the greyhound. J Appl Physiol 1979;47:290–5.
14. Winso O, Biber B, Martner J. Effects of hyperventilation and hypoventilation on stress-induced intestinal vasoconstriction. Acta Anaesthesiol Scand 1985;29:726–32.
15. Gilmour DG, Douglas IHS, Aitkenhead AR, Hothersall AP, Horton PW, Ledingham IM. Colon blood flow in the dog: effects of changes in arterial carbon dioxide tension. Cardiovasc Res 1980;14:11–20.
16. Lautt WW, Legare DJ, D'Almeida MS. Adenosine as putative regulator of hepatic arterial flow (the buffer response). Am J Physiol 1985;248:H331–8.
17. Bohrer SL, Rogers EL, Koehler RC, Traystman RJ. Effect of hypovolemic hypotension and laparotomy on splanchnic and hepatic arterial blood flow in dogs. Curr Surg 1981;38:325–8.
18. Greenway CV, Stark RD. Hepatic vascular bed. Physiol Rev 1971;51:23–65.
19. Richardson PDI, Withrington PG. Liver blood flow. Gastroenterology 1981;81:159–73.
20. Gelman S, Ernst E. The role of pH, PCO_2 and O_2 content of the portal blood in hepatic circulatory autoregulation. Am J Physiol 1977;233:E255–62.
21. Burczynski FJ, Pushka KL, Sitar DS, Greenway CV. Hepatic plasma flow: accuracy of estimation from bolus injections of indocyanine green. Am J Physiol 1987;252:H953–62.
22. Burczynski FJ, Greenway CV, Sitar DS. Hepatic blood flow: accuracy of estimation from infusions of indocyanine green in anaesthetized cats. Br J Pharmacol 1987;91:651–9.

Effects of Hypocapnia and Hypercapnia on Splanchnic Circulation and Hepatic Function in the Beagle

Yoshihisa Fujita, MD, Takayuki Sakai, MD, Akiyuki Ohsumi, MD, and Masuhiko Takaori, MD

FUJITA Y, SAKAI T, OHSUMI A, TAKAORI M. Effects of hypocapnia and hypercapnia on splanchnic circulation and hepatic function in the beagle. Anesth Analg 1989;69:152–7.

The effects of mild hypocapnia ($Paco_2$ 22 mm Hg) and hypercapnia ($Paco_2$ 59 mm Hg) on the splanchnic circulation and hepatic function were studied in six pentobarbital anesthetized, laparotomized, mechanically ventilated beagles. Tidal volume and respiratory frequency were held constant throughout the measurements. Hepatic artery blood flow (HABF) and portal vein blood flow (PVBF) were measured by electromagnetic flowmeters. Hepatic function was assessed by indocyanine green (ICG) elimination kinetic analysis after intravenous injection of the dye. Hypocapnia caused a decrease in HABF without affecting the systemic circulation. Hypercapnia, on the other hand, caused a significant increase in cardiac output without changing mean arterial pressure. There was a significant increase in PVBF and total hepatic blood flow (THBF = PVBF + HABF). Despite the increases in PVBF and THBF, the half-life of ICG was significantly longer during hypercapnia (9.09 ± 0.79 min) than during hypocapnia (7.16 ± 0.37 min), and plasma ICG clearance was smaller during hypercapnia (4.79 ± 0.44 $ml \cdot min^{-1}$) than during hypocapnia (5.44 ± 0.33 $ml \cdot min^{-1}$) or normocapnia (5.27 ± 0.50 $ml \cdot min^{-1}$), indicating the depressed hepatic function during hypercapnia. We conclude that mild hypocapnia decreases HABF without affecting hepatic function and that mild hypercapnia is associated with a depression of hepatic function in spite of the increases in PVBF and THBF.

Key Words: CARBON DIOXIDE—hypercarbia, hypocarbia. LIVER—blood flow, function.

The effects of carbon dioxide tension on the cardiovascular system have been studied extensively in dogs and humans (1–4). Hypocapnia causes vasoconstriction directly with either slight or no depression of myocardial contraction (4). Hypercapnia, on the other hand, causes a decrease in vascular resistance by direct vasodilation and an increase in myocardial contraction through stimulation of sympathetic nerve activity, resulting in a significant increase in cardiac output (1,2).

In contrast to the overall cardiovascular system, regional hemodynamic responses to alterations in $Paco_2$ are less completely understood. The regional hemodynamic response may differ from organ to organ because of the differences in vascular responsivity to $Paco_2$. Sympathetic innervation of the organs may also modify the regional hemodynamic response. In addition, $Paco_2$-induced alterations in overall cardiovascular hemodynamics also influence the regional hemodynamic response.

This study focuses on the hemodynamic responses of the splanchnic circulation to alterations in $Paco_2$, because this circulation receives the largest portion of cardiac output and plays a central role in maintaining the stability of the systemic circulation. The modification of sympathetic nerve activity caused by alterations in $Paco_2$ appears to affect the splanchnic circulation substantially, since the splanchnic vasculature is richly innervated by sympathetic nerve fibers originating from the splanchnic nerves and its importance in the regulation of the splanchnic circulation is already well recognized (5–7).

Effects of $Paco_2$ on hepatic function are also important for the preservation of hepatic function in patients during mechanical ventilation. Patients are commonly ventilated at a hypocapnic level during

---

Supported in part by Kawasaki Medical School Project Grant #62-1006 and by Grant #63480354 from the Ministry of Education for Scientific Research.

Received from the Department of Anesthesiology, Kawasaki Medical School, Okayama, Japan. Accepted for publication February 10, 1989.

Address correspondence to Dr. Fujita, Department of Anesthesiology, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-01 Japan.

©1989 by the International Anesthesia Research Society

general anesthesia or intensive therapy, whereas hypercapnia is often seen despite mechanical ventilation, especially in patients with chronic obstructive lung diseases. To the best of our knowledge, however, hepatic function during mechanical ventilation at hypocapnic or hypercapnic levels has not been assessed in conjunction with changes in the splanchnic circulation.

The present study was undertaken to elucidate the effects of alterations in $Paco_2$ on both the splanchnic circulation and hepatic function under mechanical ventilation.

Materials and Methods

The experimental protocol was approved by the institutional Animal Research committee. The study was performed in six beagle dogs of both sexes (9.4 ± 0.6 kg, mean ± SEM). Anesthesia was induced with pentobarbital 30 $mg \cdot kg^{-1}$ iv and the trachea intubated with a cuffed endotracheal tube. The animals were ventilated using a constant volume respirator (R-60, Aika, Japan) with a mixture of oxygen and nitrous oxide (1:2). Muscle paralysis was maintained with pancuronium bromide, 2 mg iv initially with half of the initial dose given again as required. Pentobarbital (60 mg) was supplemented at the end of surgical preparations, which lasted about 2 hr. Metabolic acidosis was corrected only at the end of surgical preparations by sodium bicarbonate iv using doses calculated from the base excess. Body temperature was maintained between 36.0–38.0°C with a warming blanket throughout the experiment.

Surgical Preparations

A catheter was inserted into the aorta via the femoral artery for monitoring of mean arterial pressures (MAP) and for blood sampling. A 5 Fr. flow directed three lumen thermodilution catheter (Model SP5105, Gould, USA) was inserted via the right femoral vein into the pulmonary artery. The proximal port of the catheter was placed in the thoracic inferior vena cava as confirmed by injecting contrast material under fluoroscopic monitoring. This catheter was used for determination of cardiac output (CO) by the thermodilution technique and for measurement of inferior vena cava pressure (CVP). Another catheter was advanced into the hepatic vein via the right external jugular vein, the position of which was confirmed in the same way. This catheter was used for sampling of hepatic venous blood.

A laparotomy was performed along the 12th right costal margin, and a catheter was advanced into the portal vein through a branch of the splenic veins for portal vein pressure (Ppv) measurement and blood sampling. The common hepatic artery was exposed by blunt dissection. During the dissection, we tried to keep the periarterial nerves as intact as possible, thereby preserving sympathetic control of liver blood flow. After ligation of the gastroduodenal artery and vein, cuff-type electromagnetic flow probes (6 mm and 3 mm in diameter) were applied around the portal vein and the common hepatic artery respectively, and their blood flows, portal vein blood flow (PVBF), and hepatic artery blood flow (HABF), were measured with a dual electromagnetic flow meter (MF-27, Nihon-Kohden, Japan). The accuracy of blood flow measurement using these electromagnetic flow probes had been checked previously in vitro and their calibration factors were adjusted. The zero reference was obtained by temporal clamp of the vessels in vivo at the beginning of the experiment. Total hepatic blood flow (THBF) was derived from the sum of PVBF and HABF.

Assessment of Hepatic Function

Hepatic function was assessed by indocyanine green (ICG) elimination kinetic analysis as described by Matuschak et al. (8). ICG in a dose of 0.25 $mg \cdot kg^{-1}$ was rapidly injected into the inferior vena cava through the proximal portion of the three lumen pulmonary artery catheter. Arterial blood samples were withdrawn 2, 4, 6, and 8 min after injection. The plasma concentrations of ICG were determined at 805 nm using a spectrophotometer (100-60 Type, Hitachi, Japan). The hepatic function variables including the half-life of ICG($ICG_{t1/2}$), distribution volume (Vd), and fractional clearance of ICG($C_{P,ICG}$), were calculated using a one-compartment open model (8,9).

Experimental Protocol

The respiratory rate was fixed at 20 breaths per minute. Tidal volume was adjusted to obtain normocapnia ($Paco_2$ = 38–42 mm Hg) by adding a 97 mL dead space to the endotracheal tube. Hypocapnia was induced by ventilation without the dead space and hypercapnic ventilation was induced by adding carbon dioxide to the inspired gas to maintain the $Paco_2$ around 60 mm Hg without changing the tidal volume. The adjustment of carbon dioxide flow was aided by measurement of end-tidal Pco_2 using an infrared carbon dioxide analyzer (Medical gas analyzer LB-2, Beckman, USA). Normocapnic ventilation was carried out for 60 min before starting the study. The study was performed at three different levels of $\mathrm{Paco_2}$: hypocapnia, normocapnia, and hypercapnia. The order of the three ventilatory conditions was randomized using a Latin square sequence. Each ventilatory condition was maintained for 50 min. Hemodynamic measurements and blood samplings were performed at 30 min and ICG was injected at 40 min, followed by serial arterial samplings for determination of the ICG concentrations. Arterial and venous pressures were measured during the end-expiratory phase.

Calculations

Oxygen contents in peripheral arterial, portal, and hepatic venous blood were calculated using the following formula: Oxygen content (ml·100 $\mathrm{mL^{-1}}$ blood): $C = 1.34 \times \mathrm{Hb} \times \%\mathrm{Sat} + 0.003 \times \mathrm{Po_2}$.

Hemoglobin saturation was calculated from $\mathrm{Po_2}$ corrected for pH and temperature by the $\mathrm{Po_2}$-oxygen % saturation nomogram. Oxygen delivery to the liver ($\mathrm{O_2}$h.del), oxygen uptake by the liver ($\mathrm{O_2}$h.up), and the oxygen deliver/uptake ratio ($\mathrm{O_2}$del/up) were calculated from PVBF, HABF, and oxygen contents in portal vein, hepatic artery, and hepatic vein blood using the formula of Gelman et al. (10) without correction for liver weight.

Statistics

All data are presented as the means ± standard errors of the means. Statistical comparisons of data on hemodynamics, hepatic function, and blood gas tensions during normocapnia, hypocapnia, and hypercapnia were performed using two-way analysis of variance (ANOVA). Pairwise comparisons between means were done by the Fisher's least significant difference (LSD) method. Statistical significance was defined as $P < 0.05$.

Results

Blood Gas Tensions, pH, and O_2 Delivery and Uptake

Table 1. Blood Gas Tensions, pH and Oxygen Delivery and Uptake during Normo-, Hypo-, and Hypercapnic Ventilation

	Hypocapnia	Normocapnia	Hypercapnia
Arterial blood			
pH	7.51 ± 0.02*	7.37 ± 0.01	7.22 ± 0.02*†
$\mathrm{Pco_2}$ (mm Hg)	22.1 ± 1.5*	39.1 ± 1.8	59.6 ± 3.2*†
$\mathrm{Po_2}$ (mm Hg)	141 ± 10	146 ± 6.0	141 ± 7.9
Portal venous blood			
pH	7.47 ± 0.02*	7.32 ± 0.02	7.19 ± 0.02*†
$\mathrm{Pco_2}$ (mm Hg)	28.3 ± 1.9*	46.4 ± 3.4	65.7 ± 3.2*†
$\mathrm{Po_2}$ (mm Hg)	47.2 ± 3.3*	54.7 ± 3.5	66.8 ± 6.2*†
Hepatic venous blood			
pH	7.44 ± 0.03*	7.31 ± 0.02	7.17 ± 0.02*†
$\mathrm{Pco_2}$ (mm Hg)	32.5 ± 2.6*	51.3 ± 2.8	73.2 ± 4.1*†
$\mathrm{Po_2}$ (mm Hg)	32.8 ± 3.6*	44.2 ± 3.8	50.7 ± 2.6*†
$\mathrm{O_2}$h.del ($\mathrm{mL \cdot min^{-1}}$)	40.7 ± 4.7*	52.5 ± 6.7	55.0 ± 5.5†
$\mathrm{O_2}$h.up ($\mathrm{mL \cdot min^{-1}}$)	12.3 ± 1.7	11.0 ± 1.0	9.5 ± 1.9†
$\mathrm{O_2}$del/up	3.6 ± 0.6	4.8 ± 0.5	7.3 ± 1.6†

Values are mean ± SEM.
*Significantly different from normocapnia, $P < 0.05$; †significantly different from hypocapnia, $P < 0.05$; $\mathrm{O_2}$h.del = $\mathrm{O_2}$ delivery to the liver; $\mathrm{O_2}$h.up = $\mathrm{O_2}$ uptake by the liver; $\mathrm{O_2}$del/up = $\mathrm{O_2}$ delivery to uptake ratio.

Blood gas and pH data during the three stages of ventilation are summarized in Table 1. The $\mathrm{Paco_2}$ levels were 39.1 ± 1.8, 22.1 ± 1.5, and 59.6 ± 3.2 mm Hg during normocapnia, hypocapnia, and hypercapnia respectively. Alterations in arterial $\mathrm{Pco_2}$ were accompanied by corresponding pH changes (7.51 ± 0.02, 7.37 ± 0.01, 7.22 ± 0.02). Arterial $\mathrm{Po_2}$ was, on the other hand, similar during the three stages of ventilation. Portal and hepatic venous blood pH, $\mathrm{Pco_2}$, and $\mathrm{Po_2}$ data during hypo- and hypercapnia differed significantly from those obtained during normocapnia. $\mathrm{O_2}$h.del was in the order of hypocapnia < normocapnia < hypercapnia. $\mathrm{O_2}$h.up during hypercapnia was significantly lower than during hypocapnia and $\mathrm{O_2}$del/up was significantly greater than during hypocapnia.

Effects on Systemic and Splanchnic Hemodynamics (Table 2)

During hypocapnia there were no significant changes in systemic hemodynamics. In splanchnic hemodynamics, however, HABF was significantly lower during hypocapnia (80 ± 14 $\mathrm{ml \cdot min^{-1}}$) than during normocapnia (120 ± 26 $\mathrm{ml \cdot min^{-1}}$). Hypercapnia, on the other hand, was accompanied by substantial changes in both splanchnic and systemic hemodynamics. Hypercapnia caused a significant increase in CO from 1.05 ± 0.08 to 1.23 ± 0.07 $\mathrm{l \cdot min^{-1}}$ (normocapnia and hypercapnia, respectively), while MAP was unchanged. PVBF during hypercapnia (240 ± 25 $\mathrm{ml \cdot min^{-1}}$) was significantly greater than it was during normocapnia (182 ± 13 $\mathrm{ml \cdot min^{-1}}$), whereas there

Table 2. Hemodynamic Variables during Normo-, Hypo-, and Hypercapnic Ventilation

	Hypocapnia	Normocapnia	Hypercapnia
MAP (mm Hg)	143 ± 3	142 ± 5	143 ± 4
CVP (mm Hg)	4.2 ± 0.5	4.2 ± 0.3	4.2 ± 0.4
CO (l·min^{-1})	1.09 ± 0.15	1.05 ± 0.08	1.23 ± 0.07*†
Ppv (mm Hg)	9.5 ± 0.4	10.4 ± 0.9	12.5 ± 0.8*†
HABF (mL·min^{-1})	80 ± 14*	120 ± 26	97 ± 23
PVBF (mL·min^{-1})	177 ± 17	182 ± 13	240 ± 25*†
THBF (mL·min^{-1})	252 ± 20	302 ± 31	337 ± 21*†

Values are mean ± SEM.

*Significantly different from normocapnia, $P < 0.05$; †significantly different from hypocapnia, $P < 0.05$.

MAP = mean arterial pressure; CVP = central venous pressure; CO = cardiac output; HABF = hepatic artery blood flow; PVBF = portal vein blood flow; THBF = total hepatic blood flow; Ppv = portal vein pressure.

Table 3. Hepatic Function during Normo-, Hypo-, and Hypercapnic Ventilation

	Hypocapnia	Normocapnia	Hypercapnia
$C_{P,ICG}$ (mL·min^{-1})	5.44 ± 0.33	5.27 ± 0.50	4.79 ± 0.44*†
$ICG_{t1/2}$ (min)	7.16 ± 0.37	7.78 ± 0.69	9.09 ± 0.79†
Vd (mL·kg^{-1})	55.4 ± 1.9	57.0 ± 2.8	60.6 ± 2.3

Values are mean ± SEM.

*Significantly different from normocapnia, $P < 0.05$; †significantly different from hypocapnia, $P < 0.05$.

$C_{P,ICG}$ = plasma ICG clearance; $ICG_{t1/2}$ = half-life of indocyanine green; Vd = distribution volume.

was no difference in HABF. THBF was significantly greater during hypercapnia (337 ± 21 ml·min^{-1}) than during normocapnia (302 ± 31 ml·min^{-1}). Ppv during hypercapnia was also significantly greater than it was during normocapnia (12.5 ± 0.8, 10.4 ± 0.9 mm Hg).

Hepatic Function

The results of ICG elimination kinetic analysis are summarized in Table 3. Vd, which reflects the total plasma volume, was similar during the three levels of ventilation. There were no differences in the hepatic function variables during hypocapnia and normocapnia. $ICG_{t1/2}$ was significantly longer (9.09 ± 0.79 min) during hypercapnia than during hypocapnia (7.16 ± 0.37 min) and $C_{P,ICG}$ during hypercapnia was significantly less (4.79 ± 0.44 ml·min^{-1}) than during hypocapnia (5.44 ± 0.33 ml·min^{-1}) and normocapnia (5.27 ± 0.50 ml·min^{-1}).

Discussion

Because changes in airway pressure may substantially affect splanchnic hemodynamics by changing hepatic venous pressure or compression of the liver (11,12), it was essential to maintain constant airway pressure during our study of the effects of hypo- and hypercapnia on splanchnic hemodynamics and hepatic function during mechanical ventilation. We determined the tidal volume necessary to maintain normocapnia while respiratory frequency was kept constant (20 bpm) by connecting a dead space to the endotracheal tube. Hypocapnia was achieved using the same ventilatory frequency but without the dead space, and hypercapnia occurred when CO_2 was added to the inspired gas. As a result, the tidal volume and respiratory frequency remained unchanged throughout the experiment and thus changes in airway pressure during hypocapnic, normocapnic, and hypercapnic ventilations were minimized.

Though the hemodynamic responses of the splanchnic circulation to alteration of $Paco_2$ occurs maximally in a few minutes, it stabilizes within 20 min (13). The animals in our study were, therefore, considered to be in a steady state when hemodynamic and ICG measurements were carried out.

In this study, we used pentobarbital and nitrous oxide for anesthesia, and pancuronium for muscle relaxation. The effects of these drugs, therefore, should be considered when interpreting our results. To the best of our knowledge, however, pancuronium and nitrous oxide do not significantly affect the splanchnic circulation, if at all (14). Pentobarbital IV is, on the other hand, known to cause substantial depression of the cardiovascular system. We cannot thus exclude the possibility that pentobarbital may have modified the response of the splanchnic circulation to hyper- and hypocapnia. However, we presume that it did not affect the results in this study, since pentobarbital was used only for the induction of anesthesia, i.e., about 3 hr before the measurements were begun, and because the Latin square design chosen for our study may have contributed to reduction of errors related to different anesthetic depths.

There were three major findings in this study. First, the hemodynamics in both the splanchnic and systemic circulations were not significantly affected during hypocapnia except for a decrease in HABF. Second, hypercapnia caused significant changes in both the systemic and splanchnic circulations (increases in CO, PVBF, THBF, and Ppv). Third, $C_{P,ICG}$ was less during hypercapnia than it was during normo- or hypocapnic ventilation, while $ICG_{t1/2}$ was significantly greater during hypercapnia than during hypocapnia, thus indicating a decrease in hepatic ICG uptake during hypercapnia.

It is well established that hypocapnia is associated with relatively small changes in systemic hemodynamics in anesthetized humans and animals (1,2,15). Our findings in the systemic circulation during hypocapnia are consistent with previous observations. In the splanchnic circulation, HABF decreased significantly in the present study during hypocapnia, while PVBF was unaltered.

The data in this study differ from those of Johnson (11), who reported decreases in both PVBF and HABF using electromagnetic flowmeters during hypocapnic hyperventilation in dogs. This discrepancy may be explained by the difference in the experimental conditions, since the tidal volume and respiratory frequency were changed in his experiment, while they were held constant in our study. Our results also contradict the data of Gelman et al. (16), who reported that hypocapnia increases HABF in the monkey, while cardiac output and arterial blood pressure remained unchanged, as in our study. The increase in HABF in their study was attributed to the autoregulatory response of the liver compensating for the decrease in PVBF to maintain O_2 delivery to the liver. While they used the microsphere technique for hepatic blood flow measurement without laparotomy, we measured HABF directly with an electromagnetic flow meter. It may, therefore, be possible that the surgical interventions, including laparotomy and application of electromagnetic flow probes in our study may have resulted in the different response of HABF to hypocapnia (17,18), and that the difference may be attributed to the difference in the nutritive flow (the microsphere technique) and total flow (electromagnetic flow meter).

In contrast to hypocapnia, hypercapnia caused significant changes in the systemic circulation as well as in the splanchnic circulation. Hypercapnia increased CO without affecting MAP. These results are similar to those of previous reports (2,19) and suggest the vasodilatory effect of hypercapnia and increased myocardial contraction is secondary to increased activity of the sympathetic nervous system (2).

The marked increase in PVBF during hypercapnia was considered to reflect vasodilation in the mesenteric vascular system because MAP and CVP remained unchanged. Because the mesenteric vasculature is abundantly innervated by sympathetic vasoconstrictor fibers originating from the splanchnic nerves, an increase in activity of the sympathetic nervous system should cause mesenteric vasoconstriction. The data in this study indicate, however, that the sympathetic vasoconstrictor effect does not play a major role in the splanchnic hemodynamic response during hypercapnia, and this is perhaps due to a greater direct vasodilatory effect of hypercapnia on the mesenteric vasculature.

The decrease in HABF during hypercapnia may be explained by the autoregulatory mechanism whereby the hepatic artery and portal vein adjust their flows reciprocally to maintain a constant total inflow to the liver (20). Thus, HABF may have decreased in response to the increase in PVBF during hypercapnia.

Hepatic uptake of exogenous substances is one of the most important functions of the liver. Hepatic function has been evaluated by ICG elimination kinetics by several authors (8,9), because ICG is extracted solely by hepatocytes and ICG in the doses usually used can be repeatedly administered without cellular saturation (21). ICG elimination is dependent on the liver blood flow and the ability of hepatocytes to extract the dye (22). Our data showed that $ICG_{t1/2}$ was significantly longer during hypercapnia than that during hypocapnia, and that $C_{P,ICG}$ was less during hypercapnia than normocapnia or hypocapnia. As THBF was significantly greater during hypercapnia than during hypocapnia or normocapnia, the increased $ICG_{t1/2}$ during hypercapnia appears to be an indication of the reduced ability of hepatocytes to extract the dye from blood, i.e., reduced hepatic function. Using a sulfobromophthalein, Epstein et al. (23) also observed a reduction of clearance and extraction by the liver during hypercapnia in humans, although estimated hepatic blood flow did not change significantly in their study. O_2h.up during hypercapnia in our study was also significantly less than it was during hypocapnia, though O_2h.del increased significantly during hypercapnia. The decrease in O_2h.up during hypercapnia coincides with depression of hepatic function. A similar discrepancy between THBF and ICG elimination have been reported during halothane anesthesia by Gelman et al. (9). From the ICG elimination kinetic data, they inferred that halothane affects hepatic function adversely.

Most of ICG in plasma is bound to α1-lipoproteins (24). ICG is thought to be extracted from blood into hepatocytes by carrier-mediated transport, as are other organic anions such as bilirubin and BSP, because the hepatic uptake of the anions is saturable with increasing dose, relatively selective and mutually competitive, and because countertransport of the organic anions from hepatocytes to plasma occurs (25).

There are several possible explanations for the prolongation of $ICG_{t1/2}$ and the decrease in $C_{P,ICG}$ during hypercapnia. First, acidosis during hypercapnia may be responsible for the decreased uptake of the dye. If acidosis affects the affinity of ICG for α1-lipoproteins and dissociation of the ICG becomes more difficult, a decreased ICG uptake by the hepatocytes may result without compromising hepatic function. Stollman et al. (26), however, showed that albumin binding does not affect hepatic uptake of bilirubin. For this reason, changes in the affinity of ICG for α1-lipoproteins during hypercapnia is probably not an important factor for the decreased uptake of the dye. A second explanation may be that the increased activity of the sympathetic nerve induced by hypercapnia may suppress the hepatic uptake of the dye. Recently, a close correlation between sympathetic nerve activity and hepatic function was found from the evidence that sympathetic nerve stimulation induces the hepatic glycogenolysis, which is mediated via α-receptors on the hepatocytes membrane (27). Finally, liver microcirculation may be altered by hypercapnia. Hypercapnia may dilate capillaries in the liver and thereby increase the intrahepatic shunts, which would lead to a depression of the hepatic function and an increase in THBF. If correct, this hypothesis would explain the increase in THBF, the depression of the hepatic function, and the decrease in O_2h.up.

In contrast to hypercapnia, there was no significant difference in ICG elimination kinetics during hypocapnia and normocapnia despite a decrease in HABF. This suggests that the hepatic function is preserved during mild hypercapnia.

In conclusion, we demonstrated that mild hypercapnia is accompanied by significant increases in CO, PVBF, and THBF with significant vasodilation in the systemic and mesenteric vasculature, and that mild hypocapnia has no significant effects on the systemic and splanchnic circulations except for a decrease in HABF. ICG elimination kinetic data suggest a reduction in the hepatic function to extract the dye despite the increase in THBF during hypercapnia.

We are indebted to Kaori Nakayama, PharmD for technical assistance, to Naoko Moriya for preparation of the manuscript, and to Associate Professor Seizaburo Arita of the Department of Mathematics of Kawasaki Medical School for advice and help in statistical analysis.

References

1. Price HL. Effects of carbon dioxide on the cardiovascular system. Anesthesiology 1960;6:652–63.
2. Cullen DJ, Eger E II. Cardiovascular effects of carbon dioxide in man. Anesthesiology 1974;41:345–9.
3. Prys-Roberts C, Kelman GR, Greenbaum R, Kain ML, Bay J. Hemodynamics and alveolar-arterial PO_2 difference at varying $PaCO_2$ in anesthetized man. J Appl Physiol 1968;25:80–7.
4. Theye RA, Milde JH, Michenfelder JD. Effect of hypocapnia on cardiac output during anesthesia. Anesthesiology 1966;27: 778–82.
5. Carneiro JJ, Donald DE. Changes in liver blood flow and blood content in dogs during direct and reflex alteration of hepatic sympathetic nerve activity. Circ Res 1977;40:150–7.
6. Greenway CV, Stark RD. Hepatic vascular bed. Physiol Rev 1971;51:23–65.
7. Fujita Y. Splanchnic circulation following coeliac plexus block. Acta Anaesthesil Scand 1988;32:323–7.
8. Matuschak GM, Pinsky MR, Rogers RM. Effects of positive end-expiratory pressure on hepatic blood flow and performance. J Appl Physiol 1987;62:1377–83.
9. Gelman S, Fowler KC, Smith LR. Liver circulation and function during isoflurane anesthesia and halothane anesthesia. Anesthesiology 1984;61:726–30.
10. Gelman S, Ernst E. Hepatic circulation during sodium nitroprusside infusion in the dog. Anesthesiology 1978;49:182–7.
11. Johnson EE. Splanchnic hemodynamic response to passive hyperventilation. J Appl Physiol 1975;38:156–62.
12. Hughes RL, Mathie RT, Fitch W, Cambell D. Liver blood flow and oxygen consumption during hypocapnia and IPPV in the greyhound. J Appl Physiol 1979;47:290–5.
13. Mathie RT, Blumgart LH. Effect of denervation on the hepatic haemodynamic response to hypercapnia and hypoxia in the dog. Pflügers Arch 1983;397:152–7.
14. Batchelder BM, Cooperman LH. Effects of anesthetics on splanchnic circulation and metabolism. Surg Clin North Am 1975;55:787–94.
15. Foëx P, Prys-Roberts C. Effect of CO_2 on myocardial contractility and aortic input impedance during anaesthesia. Br J Anaesth 1975;47:669–78.
16. Gelman S, Fowler KC, Bishop SP, Smith LR. Cardiac output distribution and regional blood flow during hypocarbia in monkeys. J Appl Physiol 1985;58:1225–30.
17. Gelman S. General anaesthesia and hepatic circulation. Can J Physiol Pharmacol 1986;65:1762–79.
18. Gelman S, Dillard ED, Bradley EL. Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane, or fentanyl. Anesth Analg 1987;66:936–43.
19. Hughes RL, Mathie RT, Campbell D, Fitch W. Effect of hypercarbia on hepatic blood flow and oxygen consumption in the greyhound. Br J Anaesth 1979;51:289–96.
20. Richardson PD, Withrington PG. Liver blood flow I. Intrinsic mechanism and nervous control for liver blood flow. Gastroenterology 1981;81:159–73.
21. Paumgartner G. The handling of indocyanine green by the liver. Schweiz Med Wochenschr 1975;17(suppl.):105–27.
22. Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 1975;18:378–90.
23. Epstein RM, Wheeler HO, Frumin MJ, Habif DV, Papper EM, Bradely SE. The effect of hypercapnea on estimated hepatic blood flow, circulating splanchnic blood volume, and hepatic sulfobromophthalein clearance during general anesthesia in man. J Clin Invest 1961;40:592–8.
24. Baker KJ. Binding of sufobromophthalein (BSP) sodium and indocyanine green (ICG) by plasma α1 lipoprotein. Proc Soc Exp Biol Med 1966;122:957–63.
25. Schrschmidt BF, Waggoner JG, Berk PDA. Hepatic organic anion uptake in the rat. J Clin Invest 1975;56:1280–92.
26. Stollman YR, Gaertner U, Theilmann L, Ohmi N, Wolkoff AW. Hepatic bilirubin uptake in the isolated perfused rat liver is not facilitated by albumin binding. J Clin Invest 1983;72:718–23.
27. Carceau D, Yamaguchi N, Goyer R, Guitard F. Correlation between endogenous noradrenaline and glucose released from the liver upon hepatic stimulation in anaesthetized dogs. Can J Physiol Pharmacol 1984;62:1086–91.

158 ANESTH ANALG
1989;69:158–62

Effects of Succinylcholine at the Masseter and Adductor Pollicis Muscles in Adults

Charles E. Smith, MD, FRCPC, Francois Donati, MD, PhD, FRCPC, and
David R. Bevan, MB, MRCP, FFARCS

SMITH CE, DONATI F, BEVAN DR. Effects of succinylcholine at the masseter and adductor pollicis muscles in adults. Anesth Analg 1989;69:158–62.

The effect of succinylcholine on baseline tension and evoked twitch height was measured at the masseter and the adductor pollicis muscles in ten adults undergoing elective surgery. During thiopental–nitrous oxide–enflurane (end-tidal concentration <0.25%) anesthesia, supramaximal stimulation was applied to both the ulnar nerve and the nerve to the masseter. Baseline tension and the isometric force of contraction were measured at the jaw and the thumb. Cumulative dose–response relationships were obtained by giving succinylcholine in incremental doses (initial dose, 0.10 mg/kg, followed by 0.05- or 0.1-mg/kg increments, depending on response). An infusion was started after the maximum effect of the first dose, at a rate adjusted to compensate for the rapid metabolism of the drug. There was no difference between the sensitivity of the masseter and the adductor pollicis. The ED_{50} values were (mean ± SEM) 0.11 ± 0.01 mg/kg at both muscles. The ED_{90} values were 0.17 ± 0.02 mg/kg at the masseter and 0.16 ± 0.01 mg/kg at the adductor pollicis. Onset of action was more rapid at the masseter. In six of the ten patients, baseline tension at the jaw was found to increase by a mean of 80 ± 24 g (range 25–188 g). It is concluded that in adults, masseter neuromuscular blockade can be achieved with succinylcholine doses approximately equal to those required to block the adductor pollicis In addition, the drug may cause increased tension in the muscles of the jaw.

Key Words: MONITORING—twitch tension, mandibular nerve stimulation, train-of-four. NEUROMUSCULAR RELAXANTS—succinylcholine. NEUROMUSCULAR TRANSMISSION—differential effects. SKELETAL MUSCLE—masseter, adductor pollicis.

Succinylcholine is widely employed in anesthesia to facilitate tracheal intubation. Paralysis of several muscle groups (e.g., diaphragm, vocal cords, jaw) may be important in determining the ease of intubation. However, the ulnar nerve–adductor pollicis muscle combination is commonly employed to monitor neuromuscular function (1,2). Peripheral muscles such as the adductor pollicis may exhibit differing sensitivities to neuromuscular blocking agents compared with the diaphragm (3,4), vocal cords (5) and jaw (6). As well, onset of neuromuscular blockade may vary between different muscle groups, with blockade of the diaphragm and jaw muscles preceding that of the adductor pollicis muscles (6–8).

Succinylcholine has other effects on the muscles of the jaw. It is associated with "masseter spasm," a relatively uncommon condition which is diagnosed when mouth opening and direct laryngoscopy become difficult or even impossible to perform (9,10). Recently, two reports have suggested that in the majority of children, jaw stiffness increases in response to the administration of succinylcholine, 1–2 mg/kg (11,12). In these reports, evoked adductor pollicis contraction was abolished after succinylcholine administration. However, one cannot conclude that the masseter muscle was paralyzed, because of possible differences in sensitivity to succinylcholine between jaw and thumb. The phenomenon of increased jaw stiffness has not been reported in adults.

Because of the importance of jaw relaxation for laryngoscopy and tracheal intubation, this study was designed to determine whether succinylcholine-induced increases in jaw tension occur in adults, and whether this could be explained by resistance of the masseter muscle to the neuromuscular actions of succinylcholine. To answer these questions, jaw ten-

---

Received from the Departments of Anesthesia, Royal Victoria Hospital and McGill University, Montreal, Quebec, Canada. Accepted for publication February 14, 1989.

Address correspondence to Dr. Donati, Royal Victoria Hospital, Department of Anaesthesia, 687 Pine Avenue West, Montreal, Quebec H3A 1A1, Canada.

©1989 by the International Anesthesia Research Society

sion was monitored continuously and the nerve to the masseter muscle was stimulated. Dose–response relationships were obtained for succinylcholine, both at the masseter and the adductor pollicis.

Methods

Ten adult patients, ASA physical status I or II, scheduled for elective surgical procedures were studied after institutional approval. Informed consent was obtained from each patient. Patients with neuromuscular, renal, hepatic, or electrolyte disorders or patients taking medications that were known or suspected to interfere with neuromuscular transmission were excluded. Patients with evidence of trigeminal nerve dysfunction or abnormalities of dentition or mandibular configuration were excluded from the study, as were patients with a history of atypical plasma cholinesterase or malignant hyperthermia.

Premedication was with morphine 0.1 mg/kg and glycopyrrolate 0.003 mg/kg intramuscularly 1 h before surgery. Monitors included automatic blood pressure cuff, electrocardiograph, pulse oximeter, and mass spectrometer. Anesthesia was induced with thiopental 3–5 mg/kg and fentanyl 1–2 μg/kg. The patients' lungs were ventilated by bag and mask with enflurane (1.5–2.5% end-tidal) and nitrous oxide 66% in oxygen to maintain an end-tidal CO_2 between 30 and 35 mm Hg. After tracheal intubation without muscle relaxants, enflurane was discontinued and ventilation was controlled using a semiclosed circle system with a CO_2 absorber.

The hand and forearm were immobilized in a splint. The ulnar nerve was stimulated supramaximally at the elbow using four square wave pulses of 0.2-msec duration at a frequency of 2 Hz every 12 sec. A Grass S88 stimulator and a SIU 5 isolation unit were employed. The evoked force of contraction of the adductor pollicis was measured with a Grass F10 force displacement transducer and recorded on paper. As described previously (6), the nerve to the masseter was stimulated bilaterally in the space formed by the zygomatic arch and the mandibular notch, anterior to the condyle of the mandible, using standard electrocardiograph (ECG) electrodes. The pattern of stimulation was identical to that of the ulnar nerve. This stimulation resulted in masseter muscle contraction and jaw closure. The isometric tension of the masseter muscle was measured by a force displacement transducer attached to an oral airway by a silk string. The transducer was suspended from a metal frame fixed to the operating table 10 cm caudad to the chin. The airway and the string were taped to the space between the mouth and the chin. The force registered was therefore proportional to the tension in the jaw. Supramaximal train-of-four stimulation of the nerve to masseter was assured by progressively increasing the voltage until the jaw response had stabilized. The voltage was then set 15% higher than this level.

After stabilization of baseline adductor pollicis and masseter twitch tensions, cumulative doses of succinylcholine (initial dose 0.10 mg/kg, incremental doses 0.05–0.10 mg/kg) were administered until at least 95% first twitch depression relative to first twitch control was observed. Incremental doses were given only after the effect of the previous dose had stabilized, defined as two equal consecutive train-of-four responses. To compensate for drug loss by redistribution or metabolism, a succinylcholine infusion was started once the effect from the previous dose had stabilized. The rate of infusion to replace metabolized or redistributed drug was calculated based on an estimated ED_{90} of succinylcholine of 0.22–0.30 mg/kg and an estimated dose to maintain 90% blockade by infusion of 1.70–4.68 $mg \cdot kg^{-1} \cdot h^{-1}$ (4,13–15). Assuming linear pharmacokinetics, the rate of elimination should be proportional to the dose given. Thus, the hourly rate to maintain 90% blockade is approximately 15 times the ED_{90}, and the hourly rate at which succinylcholine should be administered to compensate for elimination is 15 times the dose already given. Therefore, when the maximum effect from the first dose (0.10 mg/kg) was observed, a second dose (0.05 mg/kg or 0.10 mg/kg) was administered together with an infusion, at an hourly rate equal to the first dose times 15 (1.50 $mg \cdot kg^{-1} \cdot h^{-1}$). When the maximum effect from the second dose was apparent, a third incremental dose was given, and the infusion was set at 15 times the first two doses. Thus, the infusion rate increased linearly with the amount of drug already given. Since the amount of drug by infusion was given only to compensate for losses, only the dose administered in bolus form was considered in calculating the dose–response curves. This cumulative dose with infusion technique has been previously shown to yield dose–response curves for succinylcholine comparable to those obtained with a single bolus method (16).

When train-of-four stimulation is employed, twitch augmentation due to repetitive firing is common after depolarizing muscle relaxants are given (17). This phenomenon is usually present on the first twitch response (T1) of the train-of-four, and virtually absent on the fourth (T4) (17). Therefore, linear regressions were obtained between the logit transformation of T4 relative to control of the adductor pollicis and masseter muscle and log dose using the method of least squares (4,18). A regression line was calculated for each patient, and a mean dose–response curve was constructed. Effective doses (ED) for 50% and 90% block (ED_{50} and ED_{90}) were derived from the curves and compared between muscles using the paired Students' *t*-test. Results were expressed as mean values ± standard error of the mean (SEM). *P* values <0.05 were considered to indicate statistically significant differences.

Results

Five men and five women were studied. The mean age was 34.9 ± 3.5 yr, mean weight 70.6 ± 4.6 kg and mean height 163.9 ± 2.3 cm. Control twitch tensions were 580 ± 104 and 398 ± 59 g at the adductor pollicis and masseter muscles, respectively. Before succinylcholine administration, the end-tidal enflurane concentration was 0.18 ± 0.01%. After the initial dose, maximal blockade occurred earlier at the masseter than at the adductor pollicis muscle (1.0 ± 0.06 vs 1.2 ± 0.05 min, *P* = 0.05; end-tidal enflurane 0.14 ± 0.01%). There was no difference in time to maximum block after incremental doses (masseter 1.1 ± 0.04 vs adductor pollicis 1.1 ± 0.08 min; end-tidal enflurane 0.12 ± 0.01%). A total of two to four doses of succinylcholine were required to produce >95% neuromuscular blockade (mean dose 0.20 ± 0.02 mg/kg). The amount of succinylcholine administered as infusion was 0.05 ± 0.01 mg/kg, or 25 ± 4% of the cumulative dose. All dose–response measurements were completed within 3–5 min. There was no significant difference in the sensitivity of the two muscles to succinylcholine (Figure 1). The ED_{50} and ED_{90} values for succinylcholine at the masseter muscle were 0.11 ± 0.01 and 0.17 ± 0.02 mg/kg. Corresponding values at the adductor pollicis were 0.11 ± 0.01 and 0.16 ± 0.01 mg/kg. No patient developed evidence of phase II block, defined as a T4/T1 ratio of 0.50.

In six of the ten patients, there was an increase in masseter baseline tension (mean increase 80 ± 24 g, range 25–188 g). In three of the patients, the shift occurred 1.0 ± 0.2 min after the initial dose of succinylcholine, while the other three occurred 0.3 ± 0.1 min after the second dose. In all cases, masseter tension returned to baseline after the second dose had reached its maximal effect. This baseline shift was not present at the adductor pollicis. A similar number of patients in both groups experienced first twitch augmentation (compared to T1 control) after the initial dose of succinylcholine.

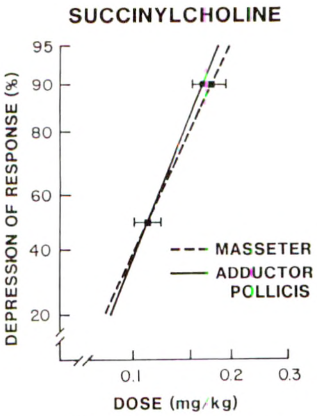


Figure 1. Depression of first twitch height, expressed as percentage of control, versus dose of succinylcholine. Bars indicate standard error of the mean for ED_{50} and ED_{90}. Lines represent linear regressions of logit transformation of neuromuscular blockade versus log dose.

Discussion

The dose–response data in the present study demonstrated that the potency of succinylcholine at the masseter and the adductor pollicis muscles was similar. In addition, onset of blockade was more rapid at the masseter than at the adductor pollicis muscle. This has been reported previously in anesthetized humans given pancuronium by means of similar methods (6), and in anesthetized cats given pancuronium, pipecuronium, *d*-tubocurarine, decamethonium, and succinylcholine (19). For example, Kharkevich and Fisenko (19) studied the comparative sensitivity of acetylcholine receptors of different skeletal muscles in cats anesthetized with urethane and chloralose and found that succinylcholine, 32 μg/kg IV, inhibited neuromuscular transmission first in the masseter muscle, then in the limb, intercostal, diaphragm, and finally in the abdominal muscles. This accelerated onset is similar to that recorded by Mircea et al. (20) in 250 adults requiring rapid sequence induction and intubation. These authors found that after succinylcholine, 2 mg/kg IV, jaw muscle relaxation occurred before the rest of the body muscles were paralyzed (20). The faster onset of both depolarizing and nondepolarizing blockade at the masseter is probably explained by its greater tissue perfusion and its closer proximity to the aorta and body core. Similarly, the earlier onset of diaphragmatic compared with adductor pollicis paralysis following succinylcholine, 0.8 mg/kg, may be due to the increased diaphragmatic blood flow favoring more rapid access of succinylcholine to the receptor (8).

In the present study, mandibular nerve stimulation and recording of masseter muscle twitch was employed in assessment of neuromuscular blockade at the masseter muscle. This type of arrangement has the advantage of permitting quantitative, continuous recording of isometric twitch tension in response to neuromuscular blocking agents. Although quantitative monitoring of mouth opening has previously been reported by Van Der Spek et al. (11,12) in humans, their technique only allows intermittent measurements and is not designed to measure isometric jaw muscle tension.

Although the three muscles that act to close the jaw (masseter, temporalis, and medial pterygoid) are all innervated by branches of the mandibular nerve (21), it is unlikely that the nerves to the temporalis and medial pterygoid muscles were stimulated to any great extent. This is because the nerve branches to these muscles run deeper than the nerve to the masseter, and the voltage setting on the stimulator for the nerve to masseter was 30% less than that of the ulnar nerve, which runs a superficial course.

The present study demonstrated an increased masseter muscle baseline tension in 60% of patients. This increase, not present at the adductor pollicis muscle, was not observed in any patient in a similar study using pancuronium in which the mandibular branch of the trigeminal nerve was stimulated and the force of masseter muscle contraction was measured (6). The mechanism of this increase in tension is not known. However, this study indicates that the sensitivity of the masseter muscle to succinylcholine is not noticeably different from that of the adductor pollicis. This suggests that masseter tension increases and masseter rigidity reported with doses of 1–2 mg/kg (9–12) are probably not due to incomplete neuromuscular blockade since the doses used were considerably greater than the ED_{90} reported in this study (0.17 mg/kg). The clinical significance of the shift in masseter muscle baseline tension is uncertain, although it has been suggested that it may represent a subclinical manifestation of masseter muscle spasm and rigidity (11,12). The variability of the response (increases a masseter tension ranging from 0 to 188 g) to the same dose of succinylcholine suggests that a small number of patients might exhibit a quantitatively abnormal response, of sufficient magnitude to be detected by the anesthesiologist. However, none of the patients in the present study developed clinical signs of masseter muscle rigidity or malignant hyperthermia.

The validity of the cumulative dose technique with infusion for short acting muscle relaxants such as succinylcholine has been demonstrated previously (16). The infusion is necessary to fulfill the requirement that redistribution and metabolism of the study drug be negligible during the period of incremental dose administration in order not to underestimate potency (16). The cumulative dose with infusion technique permits the study of one or more muscles of differing or similar sensitivities to neuromuscular blocking agents at a variety of dosage levels in the same patient. It thus eliminates the problem of whether to include or reject neuromuscular responses of 0 and 100% that may be produced by single boluses, and allows construction of a dose–response curve in every patient so that fewer total patients are required to obtain statistically valid results.

The greater potency of succinylcholine at the adductor pollicis in this study (ED_{90} = 0.16 mg/kg) compared with previous studies may be due to the different anesthetic techniques employed. For example, during halothane anesthesia the ED_{90} at the adductor pollicis was 0.21 mg/kg (4), whereas during thiopental–nitrous oxide–fentanyl anesthesia it was 0.29 mg/kg (16). Although enflurane was discontinued in the present study following tracheal intubation with resultant negligible end-tidal concentrations, it is possible that significant concentrations persisting at the neuromuscular junction may have been sufficient to potentiate the effects of succinylcholine.

During tracheal intubation, it is desirable that oropharyngeal and jaw muscles be relaxed to ensure a clear view of the vocal cords, and that respiratory muscle paralysis should prevent coughing and bucking. The present data suggest that clinically used doses of succinylcholine (1–1.5 mg/kg) are equivalent to 5–7.5 times the ED_{90} of both the masseter and the adductor pollicis muscles. Since the time-course of neuromuscular blockade of the masseter muscle after succinylcholine administration would probably reflect that of the well-perfused upper airway and diaphragm muscles, mandibular nerve stimulation may offer insight into the early onset of ideal intubating conditions, especially in cases where the ulnar nerve-adductor pollicis combination is not available for monitoring. However, care must be taken to protect the teeth, tongue, and lips from any possible damage resulting from jaw closure. Further studies are needed to delineate more clearly the utility of mandibular nerve stimulation in clinical practice. Succinylcholine-induced increases in masseter muscle baseline tension in adults anesthetized with thiopental–fentanyl–nitrous oxide–enflurane are usually small and are expected to be overcome easily by the laryngoscopist. This change in masseter muscle tension deserves further attention, however, especially in the pediatric population where the incidence of masseter muscle spasm is reported to be as high as

1% after induction of anesthesia with halothane followed by succinylcholine (9).

References

1. Lee C, Katz RL. Neuromuscular pharmacology: a clinical update and commentary. Br J Anaesth 1980;52:173–88.
2. Ali HH, Savarese JJ. Monitoring of neuromuscular function. Anesthesiology 1976;45:216–49.
3. Donati F, Antzaka C, Bevan DR. Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. Anesthesiology 1986;65:1–5.
4. Smith CE, Donati F, Bevan DR. Potency of succinylcholine at the diaphragm and the adductor pollicis. Anesth Analg 1988; 67:625–30.
5. Gilly H, Redl G, Werba A, Streinzer W, Draxler V, Spiss CK. Pharmacodynamics of vecuronium in two muscle groups: vocal cord versus thenar neuromuscular blockade in man (abstr). Anesthesiology 1987;67:A614.
6. Smith CE, Donati F, Bevan DR. Differential effects of pancuronium on masseter and adductor pollicis muscles. Can J Anaesth 1988;35:S124.
7. Chauvin M, Lebrault C, Duvaldestin P. The neuromuscular blocking effect of vecuronium on the human diaphragm. Anesth Analg 1987;66:117–22.
8. Pansard JL, Chauvin M, Lebrault C, Gauneau P, Duvaldestin P. Effect of an intubating dose of succinylcholine and atracurium on the diaphragm and the adductor pollicis muscle in humans. Anesthesiology 1987;67:326–30.
9. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: incidence and implications. Anesthesiology 1984; 61:772–75.
10. Carroll JB. Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. Anesthesiology 1987;67:559–61.
11. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effect of succinylcholine on mouth opening. Anesthesiology 1987;67:459–65.
12. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. Increased masticatory muscle stiffness during limb muscle flacidity associated with succinylcholine administration. Anesthesiology 1938;69:11–16.
13. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EL. Comparative neuromuscular effects of pancuronium, gallamine and succinylcholine during forane and halothane anesthesia in man. Anesthesiology 1971;35:509–14.
14. Cook DR. Pharmacokinetics of succinylcholine in infants, children, and adults. Clin Pharmacol Ther 1976;20:493–8.
15. Ramsey RM, Lebowitz PW, Savarese JJ, Ali HH. Clinical characteristics of long-term succinylcholine neuromuscular blockade during balanced anesthesia. Anesth Analg 1980; 59:110–16.
16. Smith CE, Donati F, Bevan DR. Dose–response curves for succinylcholine: single versus cumulative techniques. Anesthesiology 1988;69:338–42.
17. Donati F, Bevan DR. Muscle electromechanical correlations during succinylcholine infusion. Anesth Analg 1984;63:891–4.
18. Norman J. Drug–receptor reactions. Br J Anaesth 1979;51: 595–601.
19. Karkevich DA, Fisenko VP. The effect of neuromuscular blocking agents on the acetylcholine receptors of different skeletal muscles. Arch Int Pharmacodyn 1981;251:255–69.
20. Mircea N, Constantinescu C, Jiana E, Constantinescu N, Daschievici, Straja D, Ungureana D, Leoreanu A. Ultrarapid induction. Acta Anaesthesiol Belg 1985;2:61–9.
21. McMinn RMH, Hutchings RT, Logan EM. Color atlas of head and neck anatomy. Chicago: Year Book Medical Publishers, 1981.

ANESTH ANALG
1989;69:163–8

Alterations in Host Defense Associated with Inhalation Anesthesia and Blood Transfusion

J. Paul Waymack, MD, Phillip Miskell, BS, and Sara Gonce, BS

WAYMACK JP, MISKELL P, GONCE S. Alterations in host defense associated with inhalation anesthesia and blood transfusion. Anesth Analg 1989;69:163–8.

Anesthesia and blood transfusions have been demonstrated to impair immune function. The present study evaluated whether these impairments led to increased susceptibility to infectious complications in two animal models. Both transfusions and anesthesia (methoxyflurane) were found to increase susceptibility to peritoneal Escherichia coli *infections. This susceptibility increased with time after the transfusions but decreased with time after anesthesia. Neither transfusions nor anesthesia altered susceptibility to an intravenous* Escherichia coli *challenge in rats.*

Key Words: ANESTHETICS, VOLATILE—methoxyflurane. TRANSFUSION—immunologic effects. IMMUNE RESPONSE—transfusions, inhalation anesthesia. INFECTION, EFFECTS OF TRANSFUSIONS AND INHALATION ANESTHESIA.

The comparatively recent developments in anesthesia and blood transfusions have provided conditions for many major advances in surgery. These techniques have enabled surgeons to perform more complicated operative procedures than what could have been imagined in the early 19th century. Initially, there was a significantly high rate of cardiac problems with the use of inhalation anesthesia and of renal failure from the infusion of incompatible blood. The demonstration by Landsteiner (1) and others of the major blood groups and the development of safer combinations of anesthetic agents have decreased these risks (2).

In the last decade, evidence has emerged that the use of both inhalation anesthesia and transfusions poses certain previously unrecognized risks to the patient. These risks include immunosuppressive sequelae (3,4).

To determine whether the immunosuppression that follows anesthesia and transfusion also increases susceptibility to infectious complications, these techniques were evaluated in two separate septic rat models.

Materials and Methods

Animals

A total of 660 adult male Lewis rats weighing ca. 200 g were used for the septic phases of this study. Thirty male A-Sogaloff Cancer Institute (ACI) rats were used as blood donors. The animals were housed in individual cages and were given food and water ad libitum throughout the study. All animals were observed for 1 week before entry into the protocol to exclude the possibility of preexisting disease. The care of all animals was in accordance with the guidelines set forth by the Animal Welfare Act and other Federal statutes and regulations relating to animals and studies involving animals and with the *Guide for the Care and Use of Laboratory Animals*, National Institutes of Health Publication 86-23.

Anesthesia

Those animals assigned to receive anesthesia were given methoxyflurane until rendered unconscious. The methoxyflurane was given by saturating several gauze sponges with the agent and placing the sponges plus each rat into an enclosed clear plastic container 23 cm in diameter and 15 cm in length. The animals required about 2–3 min in the container to be rendered unconscious. They were then removed from the container and allowed to recover from anesthesia by breathing room air. Methoxyflurane

---

These studies were supported by the Shriners of North America and the Surgical Infection Society 3M Corporation Research Award.

Received from the Shriners Burns Institute, Cincinnati, Ohio. Accepted for publication February 13, 1989.

Address correspondence to Dr. J. Paul Waymack, Chief, Surgical Study Branch, U.S. Army Institute of Surgical Research, Fort Sam Houston, San Antonio, TX 78234-5012.

©1989 by the International Anesthesia Research Society

CALCU

was used in this study because this anesthetic, in our previous work, was able to anesthetize rats safely without complications and because toxic levels of its metabolites are not generated during brief periods of administration. An inhalation agent was used because of the difficulty in safely administering intravenous anesthetic agents to rats. Intravenous agents were not administered intraperitoneally in that, although this technique is easy and safe, it was feared that the agents might be directly toxic to the leukocytes present in the peritoneal cavity and thus alter resistance to the peritonitis challenge in a clinically irrelevant manner.

Transfusions

Blood was obtained from the donors by cardiac puncture. The blood was mixed at a 4:1 volume ratio with standard citrate–phosphate–dextrose–adenine anticoagulant and was stored at 4°C for 1 day before infusion. The transfusions were given intravenously at a dosage of 0.5 mL per animal. Previous studies had determined that blood harvested in this manner did not exhibit any measurable hemolysis.

Controls

Animals assigned to the control group received 1.5 mL per animal of normal saline administered intravenously. The threefold increase in the volume of crystalloid administered in the control group compared with the volume used in the transfusion groups was chosen since it was felt that this would most closely approximate the intravascular volume changes seen with the use of 0.5 mL of whole blood in the transfusion group. Animals in the anesthesia groups were also given 1.5 mL of saline. There were no syngeneic (pseudoautologous) transfusion control groups since the results utilizing such groups has previously been demonstrated to yield results which are statistically indistinguishable from saline controls (4).

Bacteria

The strain of *Escherichia coli,* which was supplied by Dr. Richard Simmons, was initially isolated from a human infection at the University of Minnesota Hospitals and has been demonstrated to be able to cause a lethal peritoneal infection in rats. The *E. coli* was incubated for 18 hr at 37°C in standard trypticase soy broth and was washed three times in normal saline to remove any free endotoxin. Appropriate dilutions were made with the normal saline to achieve a final concentration of 1×10^8 or 1×10^7 colony-forming units/mL of normal saline. The *E. coli* was administered in one of two septic models. In the first, 1 mL of the 1×10^7 cfu/mL suspension was administered intraperitoneally through a 22-gauge needle into the Lewis rats. In the second model, 1 mL of the 1×10^8 cfu/mL suspension was administered intravenously through the dorsal penile vein.

Treatment Groups

There were 12 separate treatment groups for each of the two septic models ($n = 20$ animals per group in intravenously challenged models and $n = 22$ in intraperitoneally challenged models). In six of these, blood transfusions were administered intravenously at varying time periods before septic challenge. These time periods were 3, 6, 5, 4, or 3 days before and on the day of septic challenge. Six groups were given anesthesia 7, 6, 5, 4, or 3 days before or on the day of septic challenge. There was also a final group for both septic models that received saline and were used as the control groups ($n = 72$ for intravenously challenged model, $n = 84$ for intraperitoneally challenged model).

Animals receiving the intraperitoneal challenge were observed for 3 days after the *E. coli* administration. With this model, animals surviving to 3 days had no further mortality and were assigned a survival time of 8 days for statistical analysis.

Animals receiving the intravenously administered *E. coli* were observed for 10 days after the septic challenge. Animals surviving to 10 days had no further mortality and were assigned a survival time of 10 days for statistical analysis.

Statistical Analysis

All data were analyzed on the University of Cincinnati CLINFO computer system. Both mean survival time ± SEM and percent survival were calculated. Statistical significance was calculated using Chi square analysis, Fisher's exact test, and the Wilcoxon test.

Results

Neither blood transfusions nor anesthesia significantly altered survival in animals that were subse-

Table 1. Mean Survival Times (± SEM) and Rates (%) in Rats Challenged with Intravenous *Escherichia coli*

	Time from treatment to challenge (days)					
	7	6	5	4	3	0
Anesthesia	3.65 ± 0.68 (15)	5.40 ± 0.88 (40)	5.40 ± 0.90 (40)	2.95 ± 0.71 (15)	3.30 ± 0.72 (15)	4.25 ± 0.89 (30)
Transfusion	4.85 ± 0.88 (35)	3.50 ± 0.78 (20)	4.30 ± 0.93 (30)	4.30 ± 0.83 (25)	4.80 ± 0.89 (35)	4.00 ± 0.69 (15)

Mean survival time was 4.67 ± 0.45 days, and survival rate was 31% for control rats.

Table 2. Mean Survival Times (± SEM) and Survival Rates (%) in Rats Challenged with Intraperitoneal *Escherichia coli*

	Time from treatment to challenge (days)					
	7	6	5	4	3	0
Anesthesia	6.55 ± 0.53 (73)	5.95 ± 0.59 (59)	5.32 ± 0.59[a] (45)[a]	6.77 ± 0.49 (73)	5.41 ± 0.62[a] (45)[a]	4.50 ± 0.75[a] (45)[a]
Transfusion	4.41 ± 0.68[a] (21)[b]	5.36 ± 0.67 (55)	6.18 ± 0.58 (64)	6.82 ± 0.43 (64)	6.05 ± 0.63 (68)	5.86 ± 0.59 (59)

Mean survival time was 6.55 ± 0.25 days, and survival rate was 68% for control rats.

[a] $P = 0.05$ vs control group.

[b] $P < 0.05$ vs control group.

quently challenged with the intravenously administered *E. coli*. Control rats that received normal saline had a 31% survival rate and a mean survival time of 4.67 ± 0.45 days. The mean survival times and survival rates for the intravenously challenged animals are shown in Table 1.

Both anesthesia and blood transfusions altered survival rates and mean survival times in rats challenged intraperitoneally with *E. coli* (Table 2). In the control rats which received normal saline before intraperitoneal *E. coli* challenge, there was a mean survival time of 6.55 ± 0.25 days. The mean survival time was significantly decreased in rats given blood transfusions 7 days before septic challenge. These rats had a mean survival time of 4.41 ± 0.68 days ($P = 0.002$ vs saline control).

Anesthesia also decreased mean survival times. This alteration was most significant as the anesthesia was administered closer to the time of septic challenge. When the anesthesia was administered 5 days before the challenge, the mean survival time was 5.32 ± 0.59 days ($P = 0.041$ vs saline control). The mean survival time when anesthesia was given 3 days before challenge was 5.41 ± 0.62 days ($P = 0.045$). Anesthesia administered on the day of septic challenge decreased the mean survival time to 4.50 ± 0.75 days ($P = 0.004$).

Survival rates were also significantly altered in rats given either anesthesia or blood transfusions and then challenged intraperitoneally (Table 2). The survival rate in the control rats that received saline was 68%. Those rats transfused 7 days before septic challenge had a 21% survival rate ($P = 0.02$ vs saline group).

The percent survival in rats given anesthesia was also most significantly impaired when the anesthesia was administered closer to the time of septic challenge. When the anesthesia was administered 5 or 3 days before challenge or on the day of challenge, the survival rate decreased to 45% ($P = 0.05$).

Discussion

Surgical patients suffering sepsis, malnutrition, and thermal injuries frequently develop various degrees of immunosuppression. Such immunodeficiency states predispose to potentially lethal infectious complications (5). Surgical patients may also require inhalation anesthesia and blood transfusions.

Our model demonstrated an increased susceptibility to bacterial infections after the administration of inhalation anesthesia. Extrapolation of this finding to include all types of anesthesias cannot safely be made based solely on our data. We did not evaluate the effect of intravenous anesthetic agents in our rat model because of the difficulties described above. Additionally, our choice of inhalation agent, although safe in rats when administered for short periods as in our model, is no longer used in humans owing to its nephrotoxicity with prolonged administration. Nonetheless, we did demonstrate that, at least in one type of animal model, one type of inhalation agent increases susceptibility to bacterial infections. Such a finding is consistent with previous human studies which demonstrated that general anesthesia impairs various components of the body's immune system. Slade and others (3) demonstrated an impairment in the patient's cell-mediated immune system as measured by skin response to intradermally applied antigens, a decrease in the blood lymphocyte count, and an impairment in lymphocyte blastogenic response to mitogen stimulation after the induction of anesthesia. This immunosuppression was seen in normal, healthy, living related kidney donors who had no evidence of any preexisting underlying disease, and was found to begin with the induction of general anesthesia.

It has also been recognized that blood transfusions impair immune function (4). The earliest evidence of this immunosuppression was noted in transplant surgery. Transplant patients given pretransplant blood transfusions have a more prolonged allograft survival than do nontransfused patients due to the transfusion-induced immunosuppression (6–10).

More recently, patients with malignancies given perioperative blood transfusions had a higher incidence of tumor recurrence, presumably due to the posttransfusion immunosuppression (4). By 1987, there were 11 reports on this phenomenon (11–23). These reports included recurrence rates associated with blood transfusions in patients with cancers of the colon (11–16), lung (17,18), and breast (19,20) as well as with sarcomas (21). In three of these reports, the transfusions failed to alter the rate of tumor metastases or decrease long-term survival rates (15, 16,20). The remaining eight papers demonstrated an increased rate of tumor recurrence and metastases in patients who received perioperative blood transfusions (11–14,17–19,21). It could be argued that, in all of these studies, the poorer results in transfused patients were due to the requirements of the patients with the more advanced tumors for a greater proportion of the transfusions and not to any immunosuppressive nature of the transfusions. This criticism is probably not valid for two reasons. First, most of the above retrospective studies separately analyzed patients based on their tumor, nodal, or metastases stage and were able to show differences in the detrimental effect of transfusions in the different stages of disease. Secondly, in studies in which rats were given an identical amount of a tumor (sarcoma) burden, with half being transfused and the remaining half given saline, transfused rats had decreased survival rates and increased rates of tumor growth (22).

Christou and others (23) studied the effects of blood loss on immune function in patients with gastrointestinal bleeding who required surgical intervention and found a positive correlation between infection rates and the use of blood transfusions. They further noted that patients who received blood transfusions had a decreased cell-mediated immune function as measured by skin testing. The immunosuppression was attributed to the hypovolemia resulting from the gastrointestinal bleeding which had necessitated the transfusions. In light of more recent work on the immunologic sequelae of transfusions, it may be that the transfusions were, at least in part, a cause of the higher infection rate.

Tartter and others (24) analyzed risk factors for the development of infections after colon surgery. They found rates of infectious complications higher in patients given transfusions in the perioperative period than in nontransfused patients with the same type of tumor and surgery. They failed to note any adverse effect on infection rates owing to age, blood loss, or duration of operation.

Blood transfusions in nonsurgical patients also impair components of the immune system. These include a decrease in the OKT4/OKT8 (helper/suppressor) T-lymphocyte ratio in patients with sickle-cell anemia and hemophilia who require transfusions (25,26). In such patients, there is also inhibition of their natural killer cell activity (27).

Although all of these studies provide strong evidence that transfusions do indeed immunosuppress patients and render them at increased risk for the development of infectious complications, it could still be argued that it was not the transfusions that caused the immunosuppression. This is because of the inability to prove that, except for receiving blood products, the two patient groups (transfused and nontransfused) were otherwise identical. Animal studies have been able to achieve this goal since the groups of transfused and nontransfused rats were identical except that one had received blood.

One of the initial animal model studies reported that allogeneic blood transfusion from an ACI to Lewis rat model caused significant impairment in macrophage function. This study demonstrated an impaired cell-mediated immune response in animals receiving allogeneic transfusions (28). The transfusions also decreased the migration of macrophages into the peritoneal cavity in response to inflammatory stimuli. Macrophages obtained from allogeneically transfused rats were found to have significant alterations in their metabolism of arachidonic acid (29). These alterations included a 50% increase in the production of thromboxane and prostacyclin and a 150% increase in the production of prostaglandin E compared with the production by macrophages obtained from nontransfused rats. The increase in prostaglandin E production was also present in traumatized rats given allogeneic blood transfusions (30). There were no alterations in the production of the immunostimulatory leukotrienes B4 or C4 after the administration of allogeneic blood (29). Finally, macrophages obtained from allogeneically transfused rats inhibited normal lymphocyte blastogenesis in response to mitogen stimulation (31).

Blood transfusions also increase the mortality rate in a burn sepsis rat model (32). This effect was seen only with allogeneic transfusions and not with syngeneic transfusions. Increasing the number or volume of the transfusions failed to increase significantly the mortality rate over that seen with a single transfusion (33).

The thermal injury used in that burn sepsis model induces a moderate degree of immunosuppression by itself. To determine whether blood transfusions alone could induce an immunodeficient state sufficient to increase susceptibility to potentially lethal infections, the model described in the present study was used. A methoxyflurane anesthesia group was added to the transfusion and saline control groups to quantitate the degree of increased susceptibility to infectious complications resulting from anesthesia. This allowed a comparison of the degree to which each agent, transfusions or anesthesia, altered resistance to infections.

Two types of septic challenge were used, an intraperitoneal and an intravenous bacterial injection, to allow for a comparison of alterations in local and systemic resistance to infection. There were significant alterations noted in mean survival time and percent survival rate with the intraperitoneal challenge model. In the anesthesia group, the more closely anesthesia was administered to the time of challenge, the more severe the impairment in resistance to infection. This indicates that the anesthesia-induced immunosuppression is very short term. The immunosuppression appears to be most severe at the time of administration of the anesthesia. This is unfortunate for surgical patients since the most likely time for the initiation of an infection may be during the administration of anesthesia, i.e., at the time of operation.

Blood transfusions in the present study increased the susceptibility to peritonitis gradually over a 1-week period. This is consistent with transplantation studies which have shown that the posttransfusion immunosuppression increases during the initial week after transfusion (10). The increased susceptibility in the present study reached statistical significance 1 week after transfusion. This delay in the onset of immunosuppression indicates that the immunosuppression is probably complex and multistage in nature. It may be related to the sequelae of the alterations in prostaglandin E synthesis noted in the earlier studies. Such alterations have been shown over a period of time to increase the number of suppressor white blood cells (34).

The demonstration of an increased mortality rate in intraperitoneally challenged rats but not in intravenously challenged rats suggests that the location of the immunosuppressive defect after blood transfusions is in the local response to bacteria. This defect could be located either in the peritoneal bactericidal response or in the lymphatic system's handling of the bacteria. Further investigations in this area are indicated.

If the data in this paper can be extrapolated to humans, the delayed onset of the immunosuppression after transfusion has clinical significance. Since the immunosuppression seen after transfusions appears to increase with time over at least the first week after the administration of blood, it would appear advisable to delay blood transfusions until the last possible moment. In a patient awaiting surgery with a severe anemia, this would mean administering blood just before the induction of anesthesia rather than following the more standard protocol of administering the blood at least 1 day before surgery so that a laboratory report showing a normal hematocrit can be present in the chart before taking the patient to the operating room.

Prevention of the anesthesia-induced immunosuppression may require the development of immunostimulatory drugs. Efforts in that area appear to be nearing success (35).

References

1. Oberman HA. The evolution of blood transfusion. Univ Mich Med Cent J 1967;33:68–74.
2. Taylor G, Larson CP Jr, Prestwich R. Unexpected cardiac arrest during anesthesia and surgery: An environmental study. JAMA 1976;236:2758–60.
3. Slade MS, Simmons RL, Yunis E, Greenberg LJ. Immunodepression after major surgery in normal patients. Surgery 1975; 78:363–72.
4. Waymack JP, Alexander JW. Blood transfusions as an immunomodulator—a review. Comp Immunol Microbiol Infect Dis 1986;9:177–83.
5. Howard RJ, Simmons RL. Acquired immunologic deficiencies after trauma and surgical procedures. Surg Gynecol Obstet 1974;139:771–82.
6. Halasz NA, Orloff MJ, Hirose F. Increased survival of renal homografts in dogs after injection of graft donor blood. Transplantation 1964;2:453–8.
7. Jenkins AM, Woodruff MFA. The effect of prior administration of donor strain blood or blood constituents on the survival of cardiac allografts in rats. Transplantation 1971;12:57–60.

8. Fabre JW, Morris PJ. The effect of donor strain blood pretreatment on renal allograft rejection in rats. Transplantation 1972; 14:608–17.
9. Opelz G, Sengar DP, Mickey MR, Terasaki PI. Effect of blood transfusions on subsequent kidney transplants. Transplant Proc 1973;5:253–9.
10. Tiwari JL. Review: kidney transplantation and transfusion. In: Teraski PI, ed. Clinical kidney transplants 1985. Los Angeles: UCLA Tissue Typing Laboratory, 1985:257.
11. Burrows L, Tartter P. Effect of blood transfusions on colonic malignancy recurrence rate (lett). Lancet 1982;2:662.
12. Agarwal M, Blumberg N. Colon cancer-patients transfused perioperatively have an increased incidence of recurrence (abstr). Transfusion 1983;23:421.
13. Burrows L, Tartter P. Blood transfusions and colorectal-cancer recurrence—a possible relationship (abstr). Transfusion 1983; 23:419.
14. Foster RS Jr, Costanza MC, Foster JC, Wanner MC, Foster CB. Adverse relationship between blood transfusions and survival after colectomy for colon cancer. Cancer 1985;55:1195–201.
15. Ota D, Alvarez L, Lichtiger B, Giacco G, Guinee V. Perioperative blood transfusion in patients with colon carcinoma. Transfusion 1985;25:392–4.
16. Nathanson SD, Tilley BC, Schultz L, Smith RF. Perioperative allogeneic blood transfusions. Arch Surg 1985;120:734–8.
17. Hyman NH, Foster RS, DeMeules JE, Costanza MC. Blood transfusions and survival after lung cancer resection. Am J Surg 1985;149:502–7.
18. Tarrter PI, Burrows L, Kirschner P. Perioperative blood transfusion adversely affects prognosis after resection of Stage I (subset NO) non-oat cell lung cancer. J Thorac Cardiovasc Surg 1984;88:659–62.
19. Nowak MM, Ponsky JL. Blood transfusion and disease-free survival in carcinoma of the breast. J Surg Oncol 1984;27: 124–30.
20. Foster RS Jr, Foster JC, Costanza MC. Blood transfusions and survival after surgery for breast cancer. Arch Surg 1984; 119:1138–40.
21. Rosenberg SA, Seipp CA, White DE, Wesley RR. Perioperative blood transfusions are associated with increased rates of recurrence and decreased survival in patients with high-grade soft-tissue sarcoma of the extremities. J Clin Oncol 1985;3: 698–709.
22. Waymack JP, Chance WT. The effect of blood transfusions on immune function. IV. Effect on tumor growth. J Surg Oncol 1988;39:159–64.
23. Christou NV, Meakins JL, Gotto D. MacLean LD. Influence of gastrointestinal bleeding on host defense and susceptibility to infection. Surg Forum 1979;30:46–7.
24. Tartter PI, Quintero S, Barron DM Perioperative blood transfusion associated with infectious complications after colorectal cancer operations. Am J Surg 1986.152:479–82.
25. Gascon P, Zoumbos NC, Young NS. Immunologic abnormalities in patients receiving multiple blood transfusions. Ann Intern Med 1984;100:173–7.
26. Luban NLC, Kelleher JF Jr, Reaman GH. Altered distribution of T-lymphocyte subpopulations in children and adolescents with haemophilia. Lancet 1983;1:503–5.
27. Kaplan J, Sarnaik S, Gitlin J, Luster J. Diminished helper/suppressor lymphocyte ratios and natural killer cell activity in recipients of repeated blood transfusions. Blood 1984; 64:308–10.
28. Waymack JP, Rapien J, Garnett D, Tweddell J, Alexander JW. Effect of transfusion on immune function in a traumatized animal model. Arch Surg 1986;121:50–5.
29. Waymack JP, Gallon L, Barcelli U, Trocki O, Alexander JW. Effect of blood transfusions on immune function. III. Alterations in macrophage arachidonic acid metabolism. Arch Surg 1987;122:56–60.
30. Waymack JP, Gallon L, Barcelli U, Alexander JW. Effect of blood transfusions on macrophage function in a burned animal model. Curr Surg 1986;43:305–7.
31. Waymack JP, Balakrishnan K, McNeal N, et al. Effect of blood transfusions on macrophage-lymphocyte interaction in an animal model. Ann Surg 1986;204:681–5.
32. Waymack JP, Robb E, Alexander JW. Effect of transfusion on immune function in a traumatized animal model. II. Effect on mortality rate following septic challenge. Arch Surg 1987; 122:935–9.
33. Waymack JP, Warden GD, Miskell P, Gonce S, Alexander JW. Effect of varying number and volume of transfusions on mortality rate following septic challenge in an animal model. World J Surg 1987;11:387–91.
34. Goldyne ME, Stobo JD. Immunoregulatory role of prostaglandins and related lipids. Crit Rev Immun 1981;2:189–225.
35. Alexander JW, Babcock GF, Waymack JP. Immunotherapeutic approaches to the prevention and treatment of infection in the surgical patient. In: Howard RJ, Simmons RL, eds. Surgical infectious diseases. Norwalk: Appleton & Lange, 1987:307–17.

ANESTH ANALG 1989;69:169–73

A Comparison of EEG Determinants of Near-Awakening from Isoflurane and Fentanyl Anesthesia

Spectral Edge, Median Power Frequency, and δ Ratio

Charles W. Long, MD,* Nitin K. Shah, MD,* Christopher Loughlin, BA,*
John Spydell, PhD,† and Robert F. Bedford, MD*

LONG CW, SHAH NK, LOUGHLIN C, SPYDELL J, BEDFORD RF. A comparison of EEG determinants of near-awakening from isoflurane and fentanyl anesthesia: spectral edge, median power frequency, and δ ratio. Anesth Analg 1989;69:169–73.

To evaluate the efficacy of the computer-processed electroencephalogram (EEG) for determining near-awakening from anesthesia, 14 patients were monitored during emergence from either isoflurane or fentanyl anesthesia at the termination of major surgical procedures. The raw EEG was obtained using bilateral frontomastoid electrodes. The compressed spectral array was digitized and recorded on disk in 4-s epochs using a Tractor Northern "Nomad" processor. The EEG information was displayed in four formats: 1) the frequency-power spectrum from 1–20 Hz, 2) the 95% power frequency, 3) the 50% power frequency, and 4) the ratio of power in the 8–20 Hz frequency range to the power in the 1–4 Hz frequency range (delta ratio). During emergence from isoflurane, there were obvious changes in the EEG frequency-power spectrum that occurred several minutes before patients opened their eyes in response to verbal stimuli. Although no one descriptor of EEG activity could be shown to be superior in anticipating when patients would respond by opening their eyes, awakening was always presaged by an abrupt decrease in power in the 1–4 Hz frequency range; this resulted in a marked increase in the delta ratio value. During emergence from fentanyl anesthesia, however, there was no obvious change in the overall EEG frequency-power spectrum. However, the same numeric EEG descriptors that were predictive of awakening from isoflurane also occurred during emergence from fentanyl, even though they usually occurred within 1 min of awakening. It is concluded that EEG criteria for identifying when patients will awaken from anesthesia are more reliable with isoflurane than with fentanyl.

Key Words: BRAIN, ELECTROENCEPHALOGRAPHY. ANESTHETICS, INTRAVENOUS—fentanyl; VOLATILE—isoflurane. MEASUREMENT TECHNIQUES, ELECTROENCEPHALOGRAPHY.

Electroencephalographic (EEG) criteria that would assist in the early detection of excessively light levels of general anesthesia would be of considerable assistance to clinicians. On-line computerized spectral analysis of the EEG has facilitated the search for such criteria, and a variety of descriptors of the EEG have been suggested as indicators of anesthetic depth. Among these, spectral edge frequency (the frequency below which 95% of the EEG power resides), median power frequency (the frequency below which 50% of the EEG power resides), and ratio of power in the 8–20 Hz range to power in the delta (1–4 Hz) range (δ ratio) have been reported previously (1–3). This study was designed to compare the utility of these various descriptors of the EEG power spectrum for identifying near emergence from light isoflurane or fentanyl anesthesia, using eye-opening in response to verbal stimuli as an end point for awakening.

Methods

Fourteen female patients, mean (± SE) age 56 ± 3 years, were studied with Institutional Review Board approval and written, informed, preoperative consent. All patients were undergoing surgery for cancer of the breast (mean [± SE] duration 120 ± 13 min). Because EEG changes associated with loss of con-

---

Presented in part at the 1988 Annual Meeting of the American Society of Anesthesiologists.

Received from the *Departments of Anesthesiology and Critical Care Medicine; Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, NY, and the †Division of BioelectroDiagnosis and Neural Monitoring, University of Pennsylvania Medical Center, Philadelphia, Pa. Accepted for publication March 14, 1989.

Address correspondence to Dr. Bedford, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

©1989 by the International Anesthesia Research Society

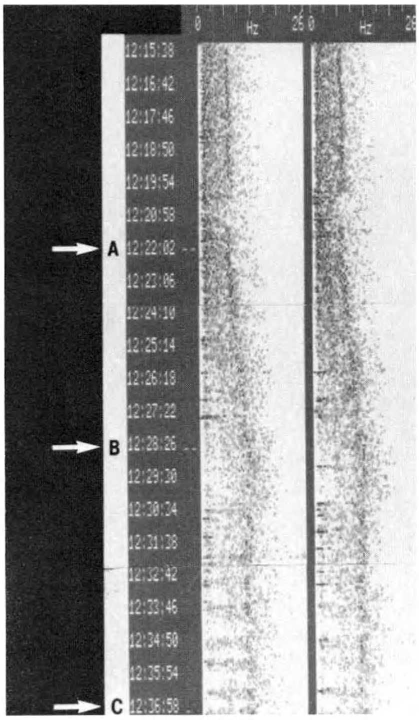


Figure 1. Representative EEG frequency-power spectrum pattern for left and right hemispheres during emergence from isoflurane. The EEG frequency is shown across the top; time moves from top to bottom (hr·min·s) in horizontal stripes indicative of four-s epochs; increasing power at a given frequency is indicated by increasingly darker dots. **Arrow A** indicates time when isoflurane was terminated. **Arrow B** indicates the abrupt shift in EEG pattern where there was loss of low-frequency activity and an increase in power at higher frequencies. **Arrow C** indicates when the patient opened his eyes on command. See text for description of EEG acquisition parameters.

sciousness occur predominantly over the frontal cortex (4), we chose to place recording electrodes in a bilateral frontomastoid array at the F3-A1 and F4-A2 positions, according to the International 10–20 nomenclature system. These electrode positions have been used successfully by other investigators for intraoperative EEG studies (5,6). Electrode impedances were always <2000 ohms. The EEG spectral analysis was performed on-line with a Tracor Northern Nomad processor. Every 4 s (1 epoch), the raw EEG signal was computer-processed using Fourier analysis. The EEG analyzer generated digital information regarding the power (μV^2) in the EEG at each frequency in the spectrum between 1 and 20 Hz. Higher frequencies were not analyzed to avoid artifact caused by frontalis muscle activity during emergence. The EEG power spectrum data were recorded throughout anesthesia and saved on disk. The median power, spectral edge, and delta ratio descriptors were computed using Tracor Northern proprietary data quantification software.

No preoperative sedation was given. Patients were anesthetized with a thiopental, nitrous oxide-oxygen, and vecuronium sequence, supplemented with either isoflurane (1% inspired) or fentanyl (1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ after an initial bolus of 5 $\mu g/kg$ intravenously [IV]). The choice of isoflurane versus fentanyl was made randomly, using an envelope method. As surgical closure began, neuromuscular blockade was reversed and N_2O was discontinued; isoflurane and fentanyl were terminated during skin closure, while minute ventilation was held constant. Once isoflurane or fentanyl was discontinued, patients were repeatedly asked to open their eyes at 15 s intervals until they were able to follow this command. End-tidal CO_2 (Criticare POET), N_2O, and isoflurane concentrations (Perkin-Elmer mass spectrometer) were recorded at the following times: 1) when the primary anesthetic was terminated, and 2) when patients opened their eyes when requested to do so.

Throughout the emergence period, each EEG variable was tabulated off-line for five consecutive, artifact-devoid epochs as follows: 1) just before the anesthetic was discontinued, 2) just before and 3) just after the EEG power spectrum abruptly changed (Fig. 1), and 4) just before patients opened their eyes in response to verbal stimuli (time "0"). The time intervals between eye opening and other data collection points were tabulated in seconds For each anesthetic, EEG data obtained at the five epoch times were subjected to statistical comparison using Wilcoxon's rank-sum test for paired data. A probability (*P*) value <0.01 represented statistical significance.

Results

Figure 1 is a representative EEG frequency-power spectrum display during emergence from isoflurane-O_2 anesthesia. Several minutes after isoflurane was discontinued, there was a sudden and marked loss of power in the 1–4 Hz range combined with an increase in power at higher (>8 Hz) frequencies. Such changes are self-evident because they occur in real time, as well. The trend analysis of the same awakening sequence (Figure 2) highlights the changes in EEG-derived parameters that typically occur between the time the primary anesthetic is terminated and the moment when awakening occurs. The frequencies below which both 50 and 95% of the EEG power reside can be seen to change gradually during emergence, whereas the δ ratio parameter changed abruptly several minutes after isoflurane was discontinued.

The EEG frequency-power spectrum pattern during emergence from fentanyl was considerably dif-

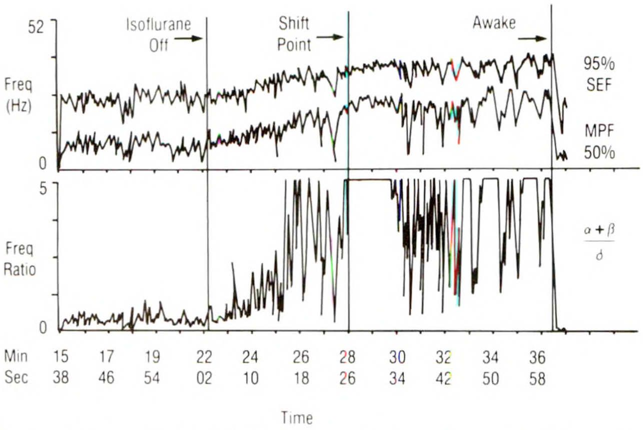


Figure 2. Trend plot of EEG-derived parameters for the same patient described in Figure 1. This emphasizes the large shift in the δ ratio ($\frac{\alpha+\beta}{\delta}$) parameter and the gradual changes in both the 50 and 95% power frequencies that occurred before the patients' awakening. MPF = median power frequency; SEF = spectral edge frequency.

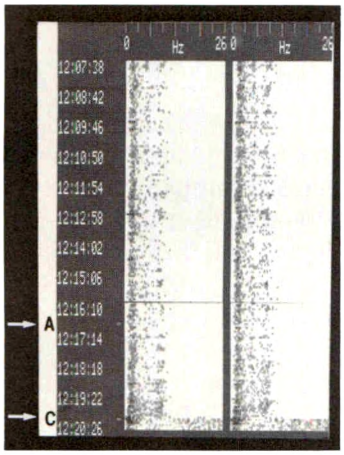


Figure 3. Representative EEG frequency-power spectrum plot during emergence from fentanyl-O_2 anesthesia. The predominance of low-frequency power (1–4 Hz) persisted from the time fentanyl infusion was terminated **(arrow A)** until eye opening occurred **(arrow C)**, when the EEG pattern is distorted by muscle movement artifact. It was not possible to identify a point that predicted awakening from fentanyl anesthesia.

ferent. In contrast to the obvious EEG changes seen during isoflurane emergence, patients anesthetized with fentanyl typically demonstrated only subtle changes in the overall EEG power spectrum until the moment of awakening, when muscle artifact tended to dominate the power spectrum (Figure 3). The derived parameters that we studied could only be seen to change during off-line analysis, but were of no use in real time for predicting when patients would awaken.

In an attempt to compare the timing of the EEG changes associated with emergence from isoflurane-O_2 and fentanyl-O_2 anesthesia, Table 1 summarizes our observations with regard to δ ratio and 50 and 95% power frequencies during emergence from both anesthetic techniques. All three EEG parameters demonstrated a statistically significant "shift" indicative of imminent awakening from both isoflurane and fentanyl. In the case of fentanyl, not only were these changes relatively subtle, but they occurred, on average, within 1 min of eye opening. In contrast, awakening from isoflurane was always presaged by large-scale changes in the EEG parameters that occurred several minutes before awakening. During emergence from both anesthetics, the magnitude of the change in the δ ratio was always more than twofold, which was considerably greater than that observed for either the 50 or 95% power frequencies.

No significant change in $P_{et}CO_2$ occurred during emergence from either anesthetic regimen, and end-tidal N_2O concentration was always <5%. End-tidal isoflurane concentration was 0.90 ± 0.11% when the agent was discontinued and 0.16 ± 0.02% when eye opening occurred.

Discussion

Light levels of general anesthesia are frequently used in combination with muscle relaxants, despite the fact that physical signs of inadequate anesthetic depth are notoriously unreliable (7). A simple real-time descriptor of near-consciousness, as determined by the computer-processed EEG, would be a potential boon to all clinicians. It would serve to avoid awareness of intraoperative events (8) and determine near-awakening during emergence from general anesthesia.

Both isoflurane and fentanyl cause EEG power in the δ range to increase markedly, coincident with decreases in α and β power (1,2). Computation of the ratio of the power in these frequency spectra magnifies this numeric descriptor and gives an end point indicative of either loss of consciousness or the near return to consciousness. In contrast, the 50 and 95% power frequencies change gradually during alterations in anesthetic depth. In real time, the gradual nature of the changes in these parameters makes it more difficult to identify near-awakening than is the case for the δ ratio parameter. Given the obvious limitations of single number descriptors and the fact that not all EEG processors can compute power spectrum ratios in real time, it is our belief that recognition of the overall pattern of the EEG power spectrum is probably the most useful technique for identifying adequate depth of anesthesia.

Table 1. Timing of Changes in EEG Frequency-Power Spectrum Descriptors during Emergence from Anesthesia

End point	95% Power frequency	50% Power frequency	δ ratio	Time (s)
		Isoflurane emergence		
Agent off	13.1 ± 0.9	5.5 ± 0.8	1.5 ± 0.7	−984 ± 103
Before shift	15.5 ± 0.6*	8.2 ± 0.6*	1.8 ± 0.3	
At EEG shift				−639 ± 71
After shift	16.3 ± 0.6*	9.2 ± 0.6*	4.1 ± 0.9*	
Awake	17.9 ± 0.4*	10.1 ± 0.9	4.7 ± 0.7	0
		Fentanyl emergence		
Agent off	12.9 ± 1.5	3.4 ± 0.6	0.4 ± 0.1	−214 ± 34
Before shift	13.2 ± 1.6	3.4 ± 0.8	0.5 ± 0.2	
At EEG shift				−51 ± 33
After shift	15.6 ± 1.0*	6.4 ± 1.1*	1.7 ± 0.6*	
Awake	16.3 ± 1.0	7.0 ± 1.6	2.7 ± 1.0	0

*$P < 0.01$ vs. previous value. δ ratio $= \frac{\text{EEG power at 8–20 Hz}}{\text{EEG power at 1–4 Hz}}$. All values are reported as mean ± SE.

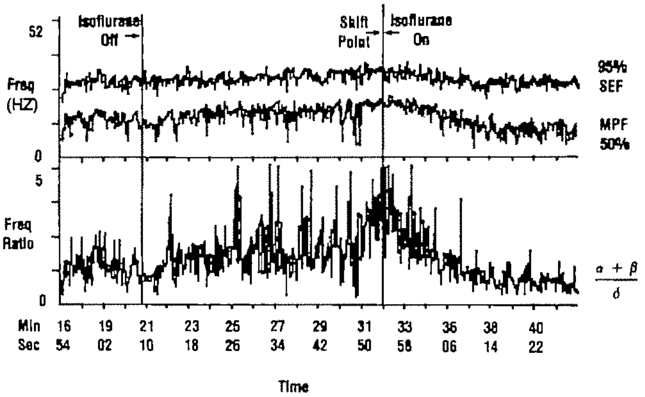


Figure 4. Trend plot of EEG-derived parameters generated during N_2O-O_2-isoflurane anesthesia with complete neuromuscular blockade and controlled ventilation ($P_{et}CO_2$ 26 mm Hg). When the end-tidal isoflurane concentration was allowed to decrease from 1.2 to 0.3%, the δ ratio parameter changed markedly and was reversed by reintroducing isoflurane into the anesthetic gas mixture. In contrast, the 95 and 50% frequency (Freq)-power changed only gradually with changes in end-tidal isoflurane concentration.

Frontalis muscle activity may produce high-frequency (>20 Hz) artifact that can be interpreted as part of the EEG power spectrum. It was for this reason that we chose to analyze EEG power only at frequencies <20 Hz. To further ensure that our observations during emergence were not simply manifestations of muscle activity, however, we briefly lightened isoflurane anesthesia intraoperatively in instances where there was complete abolition of twitch response to supramaximal ulnar nerve stimulation. Figure 4 is a representative tracing of the 50 and 95% power frequencies and δ ratio in this situation. As occurred during awakening, the magnitude of the shift in δ ratio and its change with subsequent reintroduction of isoflurane anesthesia is self-evident. Thus we believe that our findings during awakening are, in fact, representative of EEG changes and not artifact from frontalis muscle activity.

Other points on the anesthetic dose-response curve besides awakening and/or loss of consciousness have been examined using the computer-processed EEG. Levy (4) associated the onset of amnesia during induction of enflurane anesthesia with an increase in high-frequency EEG activity. This was replaced with an increase in power at low frequencies (0–4 Hz) as patients lost consciousness, although Levy did not attempt to quantitate these changes. Rampil and Matteo (9) demonstrated that hemodynamic responses to endotracheal intubation could be prevented during a thiopental-lidocaine-fentanyl-droperidol anesthetic sequence if the "spectral edge" frequency (which they defined as the highest frequency present in the EEG signal) was <15 Hz. Schwilden and Stoeckel (2) found that isoflurane-N_2O anesthesia always produced a median power frequency <5 Hz, whereas this parameter was always >5 Hz when the patients were awake. We believe, however, that the relatively gradual changes that occur with the two latter parameters render them less than ideal as clinically useful descriptors of anesthetic depth.

Evaluation of the return of near-consciousness by EEG criteria was more reliable with isoflurane than with fentanyl because with isoflurane, several minutes intervened between recognizable EEG changes and awakening. Thus, in clinical practice, it would be possible for an observant anesthetist to deepen the level of anesthesia before the patient emerges excessively. At the time of awakening, the end-tidal isoflurane concentration we observed (0.16 ± 0.02%), was, on an age-adjusted basis, essentially the same as the 0.19 ± 0.02% value identified recently by Gross and Alexander (10) as "MAC awake" for isoflurane.

In contrast to isoflurane, fentanyl is a more difficult agent for evaluation of the return of near-consciousness by EEG criteria. Not only are the changes in the EEG power spectrum pattern more subtle, but the brief interval between identifiable changes in derived parameters and awakening (<1 min on average) means that it is nearly impossible for the clinician to respond by deepening anesthesia before the patient awakens. In part, this is a result of the hysteresis between EEG response to fentanyl and plasma levels of drug, as noted by Scott et al. (1). They observed that the spectral edge increased abruptly just before emergence from fentanyl anesthesia, despite minimal decreases in plasma drug levels during this time. Although there are difficulties inherent in using the computer-processed EEG for determining anesthetic depth during fentanyl anesthesia, we still find it helpful to confirm that a patient with normal vital signs is adequately anesthetized by observing an EEG frequency-power spectrum with power distributed predominantly in the 0–4 Hz frequency range.

The question of intraoperative recall (as opposed to near-awakening) is exceedingly complex, and is not likely to be solved by EEG criteria alone. Levy (4) showed that during induction of anesthesia with enflurane, amnesia occurred before patients lost their responsiveness to verbal commands. Extrapolating Levy's findings to this study might tempt one to conclude that patients who are barely able to respond to verbal stimuli during emergence are also unlikely to have recall at that time. Therefore, they would be even less likely to have recall at the time of the EEG changes we have described during emergence from anesthesia.

Although our patients did not recall either awakening in the operating room or the discomfort of skin closure, there is still the possibility that some patients might be aware of intraoperative events if, during surgery, anesthesia were lightened to the level of the EEG frequency-power spectrum changes that we described. Because of the short time between the EEG changes and awakening from fentanyl, we expect that awareness would be more likely to occur during fentanyl anesthesia. In contrast, because several minutes intervene between EEG changes and awakening from isoflurane anesthesia, we feel confident that awareness would be extremely unlikely as long as the level of isoflurane anesthesia was promptly deepened in response to the EEG changes described. Clearly, however, more studies that specifically address the issue of intraoperative awareness need to be done before this question can be answered definitively.

In conclusion, we have described the use of the computer-processed EEG during emergence from two commonly used anesthetic techniques, both in terms of the overall frequency-power spectrum and single-number descriptors of the frequency-power spectrum. A readily identifiable shift in the frequency-power spectrum presages awakening, which may prove to be a useful index of impending awareness. This frequency-power spectrum shift can be quantitated in terms of a variety of single-number descriptors, although the overall power spectrum pattern is probably the most useful index of emergence from general anesthesia. If one goal of EEG monitoring is to avoid excessively light levels of general anesthesia, more time would be available to adjust to an inadequate level of isoflurane anesthesia than is the case with fentanyl anesthesia.

We thank George Wong, PhD of the Department of Biostatistics at Memorial Sloan-Kettering Cancer Center for his valuable assistance, and Tracor Northern Co. for generously donating the EEG processor used in this investigation.

References

1. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985;62:234–41.
2. Schwilden H, Stoeckel H. Quantitative EEG analysis during anaesthesia with isoflurane in nitrous oxide at 1.3 and 1.5 MAC. Br J Anaesth 1987;59:738–45.
3. Shah NK, Long CW, Bedford RF. "Delta Shift": an EEG sign of awakening during light isoflurane anesthesia. Anesth Analg 1988;67:S206.
4. Levy WJ. Power spectrum correlates of changes in consciousness during anesthetic induction with enflurane. Anesthesiology 1986;64:688–93.
5. Spackman TN, Faust RJ, Cucchiara RF, Sharbrough FW. A comparison of a periodic analysis of the EEG with standard EEG and cerebral blood flow for detection of ischemia. Anesthesiology 1987;66:229–31.
6. White PF, Boyle WA. Relationship between hemodynamic and electroencephalographic changes during general anesthesia. Anesth Analg 1989;68:177–81.
7. Ausems ME, Hug CC Jr, de Lange S. Variable rate infusion of alfentanil as a supplement to nitrous oxide anesthesia for lower abdominal surgery. Anesth Analg 1983;62:982–6.
8. Blacher RS. Awareness during surgery (editorial). Anesthesiology 1984;61:1–2.
9. Rampil IJ, Matteo RS. Changes in EEG spectral edge frequency correlate with the hemodynamic response to laryngoscopy and intubation. Anesthesiology 1987;67:139–42.
10. Gross JB, Alexander CM. Awakening concentrations of isoflurane are not affected by analgesic doses of morphine. Anesth Analg 1988;67:27–30.

Normovolemic Hemodilution and Lumbar Epidural Anesthesia

Stéphane Mouren, MD, Jean-François Baron, MD, Bertrand Hag, MD,
Martine Arthaud, Pharm D, and Pierre Viars, MD

MOUREN S, BARON JF, HAG B, ARTHAUD M, VIARS P. Normovolemic hemodilution and lumbar epidural anesthesia. Anesth Analg 1989;69:174–9.

This randomized study was designed to determine the cardiovascular effects of normovolemic hemodilution and lumbar epidural anesthesia in patients scheduled for vascular surgery. The patients were randomly assigned to three different groups: group 1 (N = 10) included patients undergoing lumbar epidural anesthesia without hemodilution; group 2 (N = 10) consisted of patients with normovolemic hemodilution without epidural anesthesia; and in group 3 (N = 10) normovolemic hemodilution was produced during lumbar epidural anesthesia. The three groups included several patients with a history of either myocardial infarction or stable mild angina or treated and controlled hypertension. In group 1, the level of epidural anesthesia reached T-9 ± 1. After lumbar epidural anesthesia and 7 mL/kg colloid infusion, pulmonary capillary wedge pressure increased slightly but significantly above baseline, without significant changes either in mean arterial pressure or in cardiac index. In group 2, the same colloid infusion as in group 1 when infused before normovolemic hemodilution increased pulmonary capillary wedge pressure and cardiac index without significant effects on arterial blood pressure. Normovolemic hemodilution using a colloid solution decreased hemoglobin concentration (18%) and increased cardiac index significantly (9%). No significant change in systemic oxygen transport or in total body oxygen consumption was observed. In group 3, with anesthesia to T-9 ± 1, hemodynamic changes were as observed in group 1. After normovolemic hemodilution, hemoglobin concentration decreased significantly (15%), whereas cardiac index increased significantly (15%) without significant changes either in mean arterial pressure or in heart rate. Systemic oxygen transport and total body oxygen consumption did not change significantly. No patient experienced chest pain or electrocardiographic evidence of myocardial ischemia. These data demonstrate that the effects of normovolemic hemodilution during lumbar epidural anesthesia on hemodynamic function and oxygenation were minimal, well tolerated, and comparable to those seen during hemodilution alone.

Key Words: ANESTHETIC TECHNIQUES—epidural. BLOOD—hemodilution.

Cardiovascular effects of normovolemic hemodilution include increased cardiac index that may compensate for the decreased arterial oxygen content and thereby maintain normal systemic oxygen transport (1,2). The effects of normovolemic hemodilution during general anesthesia are well known since this association is commonly seen in the surgical setting (3–6). In contrast, cardiovascular effects of epidural anesthesia and normovolemic hemodilution are unknown. The potential adverse effects of lumbar epidural anesthesia and normovolemic hemodilution on venous return and sympathetic nervous system activity have to be considered. Nevertheless, theoretical benefits that may be associated with this combination include less intraoperative blood loss and possible decrease in the incidence of perioperative venous thrombophlebitis. The goal of this randomized study was to determine the cardiovascular effects of normovolemic hemodilution and lumbar epidural anesthesia in patients scheduled for vascular surgery.

Materials and Methods

Patient Selection

After approval by our Ethics Committee, 30 patients undergoing lumbar epidural anesthesia for vascular surgery (femoropopliteal bypass grafting) gave informed consent for the study. Criteria for inclusion in the study were an hematocrit >35% and the absence of contraindications to both lumbar epidural anesthesia and normovolemic hemodilution. We excluded

---

Received from the Department of Anesthesiology, Hôpital Pitié-Salpêtrière, Paris, France.

Accepted for publication March 13, 1989.

Address correspondence to Dr. Baron, Département d'Anesthésie-Réanimation, Hôpital Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75013 Paris, France.

©1989 by the International Anesthesia Research Society

patients with disabling or unstable angina, congestive heart failure, electrocardiographic (ECG) rhythms other than sinus, uncontrolled hypertension, major respiratory or renal disease, coagulopathy and medications with β-adrenergic antagonists or digitalis.

Protocol

Cardiac medications were discontinued 2 h before the procedure. All patients were unpremedicated and studied before surgery while in supine position. Two 14-gauge catheters were inserted in peripheral veins for blood removal and infusion. Catheters were also inserted in the lumbar space (L3–4) and in a radial artery for blood pressure measurements. A triple lumen catheter was positioned in the pulmonary artery for measurements of pulmonary capillary wedge pressure and cardiac output. After a resting period of 30 min, during which fluid infusion was limited to 50 mL/h, patients were randomly assigned to three different groups. Group 1 included 10 patients undergoing lumbar epidural anesthesia without hemodilution. In group 2, 10 patients had a normovolemic hemodilution without epidural anesthesia. In group 3, normovolemic hemodilution was produced during lumbar epidural anesthesia in 10 patients. Three sets of measurements were carried out in each group.

In group 1, after the 30-min resting period, the baseline measurements were made (T0) followed by the epidural injection of 15 mL of 2% lidocaine. During the onset of epidural anesthesia, 7 mL/kg of a colloid solution (Plasmion, a solution of gelatin with a molecular weight of 35,000) was slowly infused over 30 min to ensure minimal hemodynamic changes. At the end of the infusion, when epidural anesthesia started, the second set of measurements was obtained (T1: epidural 1). Measurements were made again 40 min after T1 (T2: epidural 2).

In group 2, after baseline measurements (T0), the same volume of colloids as in group 1 was infused in 30 min without the induction of epidural anesthesia. At the end of this volume loading, the second set of measurements was carried out (T1: vol loading) after which normovolemic hemodilution was performed (the details of the technique used to produce normovolemic hemodilution are described below). Measurements were repeated at the end of the normovolemic hemodilution (T2: hemodilution).

In group 3, baseline measurements (T0) were followed by a second set of measurements made after induction epidural anesthesia and colloid infusion as in group 1 (T1: epidural). The third set of measurements was carried out after normovolemic hemodilution as in group 2 was produced during epidural anesthesia (T2: hemodilution).

Normovolemic Hemodilution Technique

The blood volume to be withdrawn to achieve an hematocrit of 30% was calculated from preoperative hematocrit and the patient's calculated blood volume. Blood was then withdrawn from one of the large venous catheters and collected into standard citrate-phosphate-dextrose blood storage bags. Simultaneously, colloid solution (Plasmion) was infused in a ratio of 1.5 mL of colloid for each milliliter of blood withdrawn. Hemodilution was continued until the large vessel hematocrit reached 30% as controlled by repeated microhematocrit determinations. Autologous blood was reinfused during the intraoperative period when hematocrit decreased to <25%.

Measurements and Data Analysis

Each set of measurements included systolic, diastolic, and mean arterial blood pressures (SAP, DAP, and MAP, respectively), heart rate (HR), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and blood temperature (T°C). Arterial and mixed venous oxygen partial pressures (Pao_2, Pvo_2) saturations (Sao_2, Svo_2) and pH (pHa, pHv) were measured from arterial and mixed venous samples. Arterial lactate concentrations were determined. Cardiac index (CI), stroke index (SI), systemic vascular resistances (SVR), arterial and venous oxygen contents (Cao_2, Cvo_2) arteriovenous oxygen difference (A-V Do_2), systemic oxygen transport (Do_2), and total body oxygen consumption (Vo_2) were derived using standard formulas. The cephalad level of lumbar epidural anesthesia was determined by the loss of pinprick sensation.

All patients were questioned during the study about the onset of chest pain. In addition, the EKG was monitored for ST segment depression. Postoperatively, a 12-lead EKG was recorded and compared to the preoperative EKG.

Intragroup analysis for statistical significance was performed using a multifactorial analysis of variance. When appropriated, multiple range tests were performed using a Scheffe's test. Intergroup analysis was done using multifactorial analysis of covariance, when appropriated, multiple range tests were also performed by a Scheffe's test. Values are expressed as mean ± SEM.

Results

The three groups of patients were not different with regards to age (group 1, 64 ± 4 yr; group 2, 53 ± 4 yr; group 3, 55 ± 4 yr). Group 1 included two patients with a past history of mild stable angina and six patients had treated and controlled hypertension. In group 2, one patient had a past history of myocardial infarction, two suffered from mild stable angina and two were successfully treated for hypertension. Group 3 included three patients with a past history of angina and three patients with treated and controlled hypertension. There were no significant difference in baseline hemodynamic variables between the three groups of patients.

Lumbar Epidural Anesthesia (Group 1)

The cephalad level of epidural anesthesia reached T-9 ± 1 segment and ranged from T-6 to T-11. After lumbar epidural anesthesia and volume loading (T1: epidural 1), PCWP increased slightly but significantly above baseline but without significant changes in SAP, DAP, MAP, HR, or CI (Table 1; Figure 1). Systemic oxygen transport and total body oxygen consumption did not significantly change (Figure 1). Forty minutes later (T2: epidural 2), there were no changes. During the study, no patient in this group experienced chest pain or EKG evidence of myocardial ischemia.

Normovolemic Hemodilution (Group 2)

After volume loading in the absence of epidural anesthesia (T1: vol loading), PCWP and CI increased significantly but without significant changes in arterial blood pressure, systemic oxygen transport or total body oxygen consumption (Table 1 and Figure 1). Blood withdrawal (1297 ± 79 mL) simultaneously replaced by colloid infusion significantly decreased hemoglobin concentration from 12.10 ± 0.45 down to 9.91 ± 0.44 g/100 mL. After normovolemic hemodilution (T2: hemodilution), cardiac index increased significantly above baseline and T1 levels but without significant changes in arterial blood pressure. Heart rate increased slightly but significantly. No significant changes in systemic oxygen transport or in total body oxygen consumption were observed. During the study, no patient in this group experienced chest pain or EKG evidence of myocardial ischemia.

Epidural Anesthesia and Normovolemic Hemodilution (Group 3)

The cephalad level of epidural anesthesia reached T-9 ± 1 and ranged from T-6 to T-11. After lumbar epidural anesthesia and volume loading (T1: epidural), the hemodynamic changes were similar to those observed in group 1 (Table 1 and Figure 1). Blood withdrawal (1208 ± 102 ml) simultaneously replaced by colloid infusion decreased hemoglobin concentration 12.37 ± 0.22 down to 10.47 ± 0.19 g/100 mL. After normovolemic hemodilution (T2: hemodilution), cardiac index increased significantly above baseline levels without significant changes in mean arterial or in heart rate. Systemic oxygen transport and total body oxygen consumption did not significantly change (Figure 1). Intergroup analysis did not reveal significant differences in hemodynamic variables, systemic oxygen transport and global oxygen consumption when compared with the two other groups at T2. During the study, no patient had chest pain or EKG evidence of myocardial ischemia.

Discussion

This study demonstrates that the effects of the combination of lumbar epidural anesthesia and normovolemic hemodilution on hemodynamic function and oxygen delivery were minimal, well tolerated, and comparable to those observed with hemodilution alone.

Sympathetic blockade associated with lumbar epidural anesthesia induces a venous and arteriolar vasodilation (7). Accordingly, the decrease in arterial blood pressure usually observed results from a decrease in both systemic vascular resistance and cardiac index (8). It has been suggested that previous volume loading may limit these hemodynamic changes (9). In our study (groups 1 and 3), colloid infusion during the onset of epidural anesthesia maintained mean arterial pressure and cardiac index. Moreover, the same volume loading without extradural blockade induced an increase in pulmonary capillary wedge pressure and cardiac index as observed in group 2.

Studies of hemodynamic changes during normovolemic hemodilution have established that the reduction in hematocrit and in arterial oxygen content is not deleterious since compensating mechanisms maintain systemic oxygen transport and tissue oxygenation (10,11). The decrease in whole blood viscosity is associated with increases in venous return and cardiac index (12). In addition, the improvement in distribution of blood flow at the microvascular level facilitates peripheral oxygen unloading and improved oxygen extraction ratio (13,14). In group 2, after both volume loading and normovolemic hemodilution, systemic oxygen transport and total body oxygen consumption were maintained.

Table 1. Hemodynamic Variables, Blood Gas Results, and Derived Parameter

		T0	T1	T2
Gr 1		Control	Epidural 1	Epidural 2
Gr 2		Control	Vol Loading	Hemodilution
Gr 3		Control	Epidural	Hemodilution
MAP (mm Hg)	Gr 1	96.40 ± 5.77	95.70 ± 3.70	96.90 ± 2.96
	Gr 2	98.50 ± 5.39	105.00 ± 4.52	99.50 ± 3.96
	Gr 3	88.40 ± 5.43	93.60 ± 5.79	92.50 ± 4.98
HR (beats/min)	Gr 1	71.70 ± 3.34	73.50 ± 3.64	73.60 ± 2.69
	Gr 2	65.00 ± 1.99	63.80 ± 3.01	69.10 ± 2.26
	Gr 3	68.70 ± 3.05	69.40 ± 2.57	74.30 ± 3.67
PCWP (mm Hg)	Gr 1	7.00 ± 1.23	10.20 ± 0.91^{b}	9.40 ± 0.81^{b}
	Gr 2	7.30 ± 1.28	10.80 ± 0.80^{b}	9.80 ± 1.21^{b}
	Gr 3	8.00 ± 1.20	11.70 ± 0.96^{b}	11.20 ± 1.05^{b}
CI ($L \cdot min \cdot m^{-2}$)	Gr 1	4.05 ± 0.29	4.29 ± 0.20	4.24 ± 0.20
	Gr 2	3.39 ± 0.24	4.09 ± 0.28^{b}	4.45 ± 0.34^{bf}
	Gr 3	3.88 ± 0.18	4.42 ± 0.29	5.06 ± 0.39^{b}
SVR (UI)	Gr 1	23.71 ± 2.28	21.19 ± 1.10	21.78 ± 1.37
	Gr 2	28.14 ± 2.05	24.80 ± 1.67	22.32 ± 1.98
	Gr 3	22.12 ± 1.45	20.38 ± 1.57	18.28 ± 2.11
PaO_2 (mm Hg)	Gr 1	86.50 ± 10.56	86.90 ± 8.10	81.20 ± 6.33
	Gr 2	84.75 ± 2.79	85.20 ± 2.64	97.10 ± 21.64^{bf}
	Gr 3	84.70 ± 4.59	84.78 ± 2.67	86.00 ± 2.83
Hb (g/dL)	Gr 1	12.57 ± 0.51	11.74 ± 0.44^{b}	11.41 ± 0.48^{bc}
	Gr 2	13.23 ± 0.52	12.10 ± 0.45^{b}	9.91 ± 0.44^{bdf}
	Gr 3	13.65 ± 0.31	12.37 ± 0.22^{b}	10.47 ± 0.19^{bdh}
CaO_2 (mL/100 mL)	Gr 1	15.66 ± 0.61	14.65 ± 0.56^{b}	14.20 ± 0.62^{bc}
	Gr 2	16.40 ± 0.67	15.12 ± 0.53^{b}	12.54 ± 0.56^{bdf}
	Gr 3	17.12 ± 0.44	15.46 ± 0.29^{b}	13.14 ± 0.25^{bdf}
PvO_2 (mm Hg)	Gr 1	37.78 ± 1.05	35.67 ± 0.65	36.22 ± 1.10
	Gr 2	38.86 ± 0.59	39.60 ± 1.30	36.11 ± 1.09^{bd}
	Gr 3	41.60 ± 1.41	38.89 ± 0.69	38.30 ± 1.25
CvO_2 (mL/100 mL)	Gr 1	11.52 ± 0.63	10.34 ± 0.46	10.08 ± 0.51
	Gr 2	12.39 ± 0.51	11.50 ± 0.39^{b}	8.61 ± 0.44^{bdf}
	Gr 3	13.35 ± 0.48	11.61 ± 0.31^{b}	9.62 ± 0.30^{bdi}
Lactate (mmol/L)	Gr 1	1.04 ± 0.24	1.19 ± 0.27	1.18 ± 0.29
	Gr 2	0.76 ± 0.14	1.08 ± 0.17^{b}	1.24 ± 0.17^{bd}
	Gr 3	0.99 ± 0.09	1.14 ± 0.13	1.28 ± 0.14
Temperature (°C)	Gr 1	36.54 ± 0.12	36.54 ± 0.14	36.51 ± 0.18
	Gr 2	36.40 ± 0.10	36.21 ± 0.14	36.14 ± 0.15
	Gr 3	36.59 ± 0.05	36.34 ± 0.08	36.33 ± 0.10

Abbreviations Gr, group.
[a] $P < 0.05$, [b] $P < 0.01$: significant changes vs T0.
[c] $P < 0.05$, [d] $P < 0.01$: significant changes between T1 and T2.
[e] $P < 0.05$, [f] $P < 0.01$: significant changes between Gr 1 and Gr 2.
[g] $P < 0.05$, [h] $P < 0.01$: significant changes between Gr 1 and Gr 3.
[j] $P < 0.05$, [i] $P < 0.01$: significant changes between Gr 2 and Gr 3.

The association of lumbar epidural anesthesia and normovolemic hemodilution may have adverse effects on the cardiovascular system especially on venous return and activity of sympathetic nervous system. Whereas hemodilution decreases venous resistance, extradural blockade increases venous compliance and decreases venous return (7). Normovolemic hemodilution increases sympathetic cardiac tone (15) whereas lumbar epidural anesthesia decreases sympathetic tone and increases parasympathetic tone (16). The cardiovascular effects associated with lumbar epidural anesthesia and normovolemic hemodilution are not clear, however. To our knowledge, no previous work studying cardiovascular changes induced by this combination has been published. Our study shows that mean arterial pressure and heart rate are maintained during lumbar epidural anesthesia with normovolemic hemodilution. Cardiac index increased above baseline levels but systemic oxygen transport and total body oxygen consumption did not

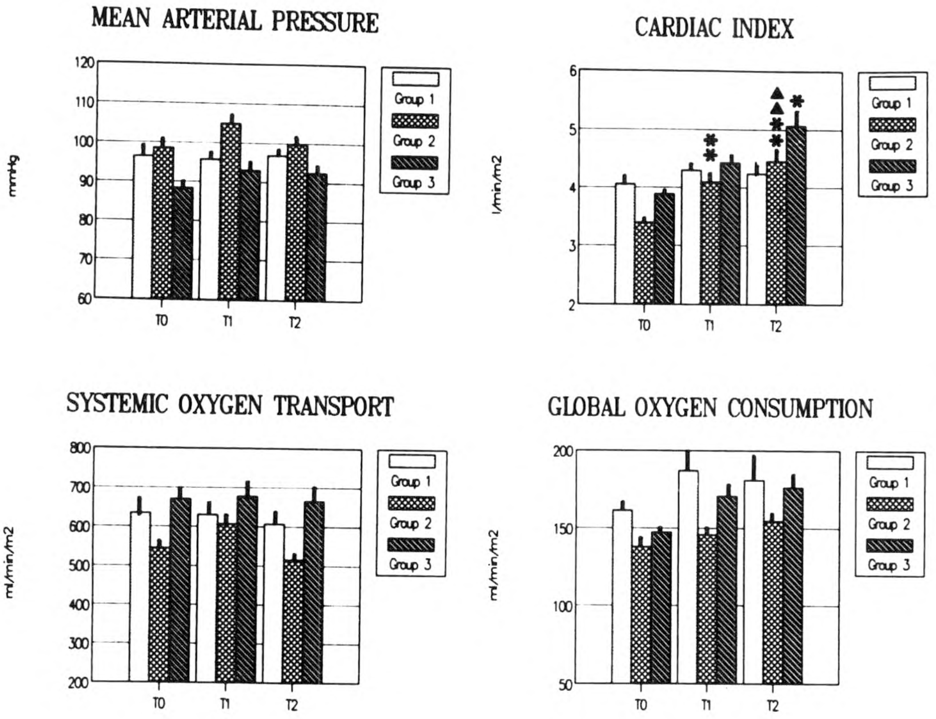


Figure 1. Mean arterial pressure, cardiac index, systemic oxygen transport and total body oxygen consumption in the three groups of patients. $^*P <$ 0.05, $^{**}P < 0.01$: significant changes vs T0. ▲ $P < 0.05$, ▲▲ $P < 0.01$: significant changes between T1 and T2.

	T0	T1	T2
Group 1	Control	Epidural 1	Epidural 2
Group 2	Control	Vol Loading	Hemodilution
Group 3	Control	Epidural	Hemodilution

change. Several mechanisms are involved in explanation of these results. Colloid infusion during the onset of epidural anesthesia increased pulmonary capillary wedge pressure and so probably minimized the effects of lumbar epidural anesthesia on venous return (7) and on cardiac vagal tone (16). Furthermore, sympathetic tone in the unblocked areas increases during lumbar epidural anesthesia and may contribute to the hemodynamic stability (17). In addition, sympathetic stimulation mediated by plasma levels of lidocaine used to induce epidural anesthesia could have played a role (18). The lack of deleterious hemodynamic effects of epidural anesthesia with normovolemic hemodilution is of special interest in view of the abnormal preoperative cardiovascular status of some of the studied patients. Myocardial ischemia did not develop, at least clinically, in the patients suffering from stable mild angina in the different groups. Indeed, lumbar epidural anesthesia has been shown to exert beneficial effect on myocardial function in patients with mild and stable coronary artery disease (19). However, the effects of normovolemic hemodilution in patients with coronary artery disease have remained in dispute since experimentally deleterious effects on coronary circulation have been reported in animals (20) though some clinical studies have failed to confirm these findings (21,22).

In the surgical setting, there are several potential benefits of the combination of extradural blockade and normovolemic hemodilution. First, since each of these two techniques has been shown to reduce thromboembolic complications (23,24), a cumulative effect might be expected. Secondly, this combination may be of use clinically since the reduction in blood loss associated with epidural anesthesia may facilitate exclusively autologous transfusion using normovolemic hemodilution (3,4,25–27). In patients undergoing vascular surgery several additional benefits on collateral flow, musculocutaneous oxygenation (10,11,28) and in early patency of peripheral vascular grafts (29) may be expected.

Our study shows that the combination of normovolemic hemodilution to an hematocrit of 30% and epidural anesthesia is not associated with adverse effects on cardiovascular function or peripheral oxygen transport. Volume loading to compensate for the effects of epidural anesthesia and a strict maintenance of normovolemia during hemodilution are essential to minimize cardiovascular effects.

References

1. Messmer K, Lewis H, Sunder-Plassman L, Klovekorn WP, Mendler N, Holper K. Acute normovolemic hemodilution. Changes of central hemodynamics and microcirculation flow in skeletal muscle. Eur Surg Res 1972;4:55–70.
2. Race D, Dedichen H, Schenk WG. Regional blood flow during dextran-induced normovolemic hemodilution in the dog. J Thorac Cardiovasc Surg 1967;53:578–85.
3. Rose D, Coutsoftides T. Intraoperative normovolemic hemodilution. J Surg Res 1981;31:375–81.
4. Laks H, Pilon R, Klovekorn WP, Anderson W, MacCallum J, O'Connors NE. Acute hemodilution: its effects on hemodynamics and oxygen transport in anesthetized man. Ann Surg 1974;180:103–9.
5. Shah DM, Prichard MN, Newell JC, Karmody AM, Scovill WA, Powers SR. Increased cardiac output and oxygen transport after intraoperative isovolemic hemodilution. A study in patients with peripheral vascular disease. Arch Surg 1980; 115:597–600.
6. Vara-Thorbeck R, Guerrero-Fernandez Marcote JA. Hemodynamic response of elderly patients undergoing major surgery under moderate normovolemic hemodilution. Eur Surg Res 1985;17:372–6.
7. Shimoshato S, Eisten BE. The role of venous system in cardiocirculatory dynamics during spinal and epidural anesthesia in man. Anesthesiology 1969;30:619–28.
8. McLean APH, Muligan GW, Otton PE, McLean LD. Hemodynamic alteration associated with epidural anesthesia. Surgery 1967;62:79–87.
9. Ramanathan S, Masih A, Rock J, Chalon J, Tunrdorf H. Maternal and foetal effects of prophylactic hydration with crystalloids or colloids before epidural anesthesia. Anesth Analg 1983;62:673–8.
10. Messmer K, Kreimeier U, Intaglietta M. Present state of intentional hemodilution. Eur Surg Res 1986;18:254–63.
11. Messmer K. Les effets de l'hémodilution sur les propriétés rhéologiques du sang et sur l'oxygénation des tissus. Anesth Analg Reanim 1976;33:509–20.
12. Guyton AC, Richardson TQ. Effect of hematocrit on venous return. Circ Res 1961;9:157–64.
13. Vicaut E, Hamidou L, Vielledent M, Vallez MO, Duvelleroy M, Teisseire B. Hemodilution effect on red cell partioning in capillary bifurcations. Int J Microcirc Clin Exp 1985;4:351–62.
14. Vicaut E, Strucker O, Teisseire B, Duvelleroy M. Effects of changes in systemic hematocrit on the microcirculation in rat cremaster muscle. Int J Microcirc Clin Exp 1987;6:225–35.
15. Glick G, Plauth WH, Braunwald E. Role of autonomic nervous system in the circulatory response to acute induced anemia in unanesthetized dogs. J Clin Invest 1964;43:2112–24.
16. Baron JF, Decaux-Jacolot A, Edouard A, Berdeaux A, Samii K. Influence of venous return on baroreflex control of heart rate during lumbar epidural anesthesia in humans. Anesthesiology 1986;64:188–93.
17. Baron JF, Payen D, Coriat P, Edouard A, Viars P. Forearm vascular tone and reactivity during lumbar epidural anesthesia. Anesth Analg 1988;67:1065–70.
18. Edouard A, Berdeaux A, Langloys J, Samii K, Guidicelli JF, Noviant Y. Effects of lidocaine on myocardial contractility and baroreflex control of heart rate in conscious dogs. Anesthesiology 1986;64:316–21.
19. Baron JF, Coriat P, Mundler O, Faucher M, Bousseau D, Viars P. Left ventricular global and regional function during lumbar epidural anesthesia in patients with and without angina pectoris. Influence of volume loading. Anesthesiology 1987; 66:621–7.
20. Hagl S, Heimlich W, Meisner H, Erben R, Baum M, Mendler N. The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. Basic Res Cardiol 1977; 72:344–64.
21. Van der Linden Ph, Baron JF, Philip I, Arthaud M, Coriat P, Bertrand M, Vicaut E, Debat P, Viars P. Normovolemic hemodilution in anesthetized patients with coronary artery disease: effects on hemodynamic and left ventricular function [abstract]. Anesthesiology 1987;67(suppl):A135.
22. Laxenaire MC, Aug F, Voisin C, Chevreaud C, Bauer P, Bertrand A. Effects of hemodilution on ventricular function in coronary heart disease patients. Ann Fr Anesth Reanim 1986; 5:218–22.
23. Gotta AW. The effects of local anesthetics on platelet agregation. Reg Anesth 1983;18:65–8.
24. Modig J, Borg T, Karlstrom G, Maripuu E, Sahlstedt B. Thromboembolism after total hip replacement: role of epidural and general anesthesia. Anesth Analg 1983;62:174–80.
25. Chin SP, Abdou-Madi MN, Eurin B, Witvoet J, Montagne J. Blood loss in total hip replacement: extradural vs. phenoperidine analgesia. Br J Anaesth 1982;54:491–5.
26. Moir DD. Blood loss during major vaginal surgery. A statistical study of the influence of general anaesthesia and epidural analgesia. Br J Anaesth 1986;40:233–40.
27. Thorund T, Lund I, Holme I. The effects of anesthesia on intra operative and post operative bleeding during abdominal prostatectomies: a comparison of neurolept anesthesia, halothane anaesthesia and epidural anaesthesia. Acta Anaesthesiol Scand 1975;57:83–8.
28. Fleckenstein W, Kersting T, Schaffler A, Heinrich R, Reinhart K, Weiss C. Effects of bleeding and hemodilution on muscular Po_2 in the dog. In: Erhly AM, Hauss J, Huch R, eds. Clinical oxygen measurement, tissue oxygen pressure and transcutaneous oxygen measurement. Berlin: Springer-Verlag, 1985: 208–15.
29. Mahir MS, Hynd JW, Flute PT, Dormandy JA. The effect of normovolemic haemodilution on the early patency rate of small calibre vascular protheses studied in a new animal model. Thrombosis Res 1986;41:771–80.

ANESTH ANALG
1989;69:180–4

Tachyphylaxis Associated with Repeated Epidural Injections of Lidocaine Is Not Related to Changes in Distribution or the Rate of Elimination from the Epidural Space

Torben Mogensen, MD, Lene Simonsen, MD, Nicholas B. Scott, FRCS (Ed),
Jens H. Henriksen, MD, PhD, and Henrik Kehlet, MD, PhD

MOGENSEN T, SIMONSEN L, SCOTT NB, HENRIKSEN JH, KEHLET H. Tachyphylaxis associated with repeated epidural injections of lidocaine is not related to changes in distribution or the rate of elimination from the epidural space. Anesth Analg 1989;69:180–4.

The relationship between tachyphylaxis (measured as a decrease in the rate of regression of sensory levels of analgesia) during repeated epidural injections of lidocaine and both the distribution of lidocaine within the epidural space (as measured by spread of simultaneous injection of the tracer technetium-99m diethylenetriaminepentaacetate [^{99m}Tc-DTPA]) and elimination of lidocaine from the epidural space (as measured by serum concentrations of lidocaine) was investigated in 18 patients undergoing minor surgery during lumbar epidural analgesia. Twelve patients received four injections of 20 mL of 2% lidocaine at 2-hr intervals. Epidural distribution was assessed by injection of ^{99m}Tc-DTPA diluted in saline on the preoperative day and diluted in an equal volume of 2% lidocaine on the morning before surgery and again after the fourth injection of lidocaine 6 hr later. The distribution of ^{99m}Tc-DTPA in the epidural space was unchanged during the three measurements despite significant tachyphylaxis in both sensory analgesia and motor blockade (11 of 12 patients had sensory analgesia 2 hr after the first injection in contrast to only 3 of 12 patients during the third injection). In another six patients 20 mL of 2% lidocaine were injected three times at 2-hr intervals before surgery, with measurements of serum concentrations of lidocaine after the first and last injections. Despite tachyphylaxis (no patient had sensory analgesia 2 hr after the third injection), there was no difference in the rate of disappearance of lidocaine from the epidural space as assessed by plasma lidocaine concentration curves during the first and third injection (0.5 ± 0.1 and 0.3 ± 0.04 $\mu g \cdot mL^{-1} \cdot min^{-1}$, respectively). The results confirm the development of tachyphylaxis during repeated epidural injections of lidocaine and suggest that tachyphylaxis is caused by factors other than increased elimination from the epidural space or altered distribution of lidocaine within the epidural space.

Key Words: ANESTHETIC TECHNIQUES—epidural. PHARMACOLOGY, TACHYPHYLAXIS—lidocaine.

Acute tolerance ("tachyphylaxis") or regression of sensory analgesia is the term used for the continuous decline in effect (i.e., shorter duration or decrease in spread of analgesia) during repeated administration of the same dose of local anesthetic. Tachyphylaxis has been demonstrated after epidural neural blockade with long-acting anesthetics such as bupivacaine (1,2) as well as with short-acting anesthetics such as lidocaine (3).

The basis for the development of this type of acute tolerance remains unclear (4,5) but may involve either decreased effect of the local anesthetic at the cellular level, decreased fraction of drug reaching the site of action because of increased elimination from the epidural space, or altered distribution within the epidural space (5). Finally, changes in the central nervous system may facilitate tachyphylaxis resulting from competitive postoperative increases in afferent input (5).

The purpose of this study was, therefore, to investigate the relationship between tachyphylaxis and distribution and elimination of lidocaine in the epi-

---

Supported by a grant from Astra Alab, Södertälje, Sweden.

Received from the Departments of Anesthesiology, Clinical Physiology/Nuclear Medicine, and Surgical Gastroenterology, Hvidovre University Hospital, University of Copenhagen, Copenhagen, Denmark. Accepted for publication March 13, 1989.

Address correspondence to Dr. Mogensen, Department of Anesthesiology, Hvidovre University Hospital, DK-2650 Hvidovre, Denmark.

©1989 by the International Anesthesia Research Society

dural space assessed by technetium-99m diethylenetriaminepentaacetate (^{99m}Tc-DTPA) and plasma lidocaine concentrations respectively.

Methods

Eighteen patients scheduled for minor surgery during epidural analgesia were studied.

The study was approved by the Ethics Committee for Medical Research in Copenhagen. Informed consent was obtained from each patient and no complication or side effects were seen.

The study was divided into two parts.

Part 1

Twelve men, mean age 70 (range 67–71) yr, height 171 (163–185) cm, weight 69 (50–87) kg, scheduled for transurethral surgery (duration 40 [20–65] min) were studied. The epidural catheter was inserted between L-2 and L-3 through which four injections of 3 plus 17 mL of 2% lidocaine without epinephrine were made at 2-hr intervals. Surgery was performed after the first injection. Levels of analgesia (pinprick) and motor blockade (0–3, according to Bromage [6]) were measured every 20 min throughout the 8-hr study period.

Distribution of ^{99m}Tc-DTPA. In 6 of these 12 patients the epidural catheter was inserted the day before surgery. The distribution within the epidural space of ^{99m}Tc-DTPA was assessed by injection of 15–20 MBq ^{99m}Tc-DTPA diluted in 17 mL of isotonic saline through the epidural catheter, 5 min after 3 mL of isotonic saline was injected as a test dose. On the next day 45 min before surgery and again 6 hr after the initial dose (the fourth dose of lidocaine), its distribution was reassessed after injection of ^{99m}Tc-DTPA diluted in 17 mL of 2% lidocaine 5 min after the test dose of 3 mL of lidocaine.

The radiation dose to the epidural space was 1 mSv.

Data Analyses. The γ emissions from the epidural space were measured externally with the patients in supine position by use of a γ camera (General Electric camera 400 zs) with a 40-cm field of view and a low-energy collimator. The recordings over the patient's back were stored in a PDP 11 digital computer, at 30-sec frames, for 30 min. The epidural area was individually outlined. The distribution of the tracer in the upper, middle, and lower parts of the epidural space viewed by the γ camera was obtained after 10 min.

No patient received additional medications for pain during the study period.

Part 2

Six patients, one woman and five men, mean age 66 (range 60–75) yrs, height 173 (164–182) cm, weight 76 (52–99) kg, were studied before surgery. An epidural catheter was inserted between L-2 and L-3 6 hr before surgery. Five min after the test dose (3 mL), 17 mL of 2% lidocaine without epinephrine was injected. The (3 + 17) mL doses were repeated two more times at 2-hr intervals. Blood samples for determination of plasma lidocaine were drawn from a central venous catheter immediately before and 1, 5, 10, 20, 40, 80, and 120 min after the first and third injections of 17 mL of 2% lidocaine. Plasma lidocaine was analyzed by gas chromatography by Astra Alab AB, Södertalje, Sweden.

The sensory level of analgesia and motor blockade were assessed every 20 min after all three injections. Results are expressed as means ± 1 standard error of the mean (SEM). Data were analyzed for statistical significance using Wilcoxon's test for paired data, χ^2-test (Yates-corrected), and Friedman's analysis of variance. $P < 0.05$ was considered statistically significant. Plasma concentrations of lidocaine associated with the first and third injections were compared by Pratt's test disregarding time. The concentrations of plasma lidocaine before the third injection were subtracted from the plasma concentrations after the third injection to determine the increase in plasma level resulting from the third injection.

Results

The changes in sensory analgesia and motor blockade in parts 1 and part 2 are illustrated in Figure 1. In both parts of the study there were clear signs of acute tolerance, "tachyphylaxis." In 9 of the 12 patients in part 1 the duration of sensory analgesia was <2 hr after the third injection of lidocaine and no patient had a measurable sensory analgesia 2 hr after the fourth injection. In contrast, 11 of 12 patients had a sensory blockade 2 hr after the first injection. The difference is statistically significant. Similarly, no patient in part 2 of the study had sensory analgesia 2 hr after the third injection. Duration of sensory analgesia was similar in the postoperative setting (part 1) and preoperative setting (part 2). There was no significant change in the rostrad spread of analgesia 20 and 40 min after any injection pre- or postoperatively.

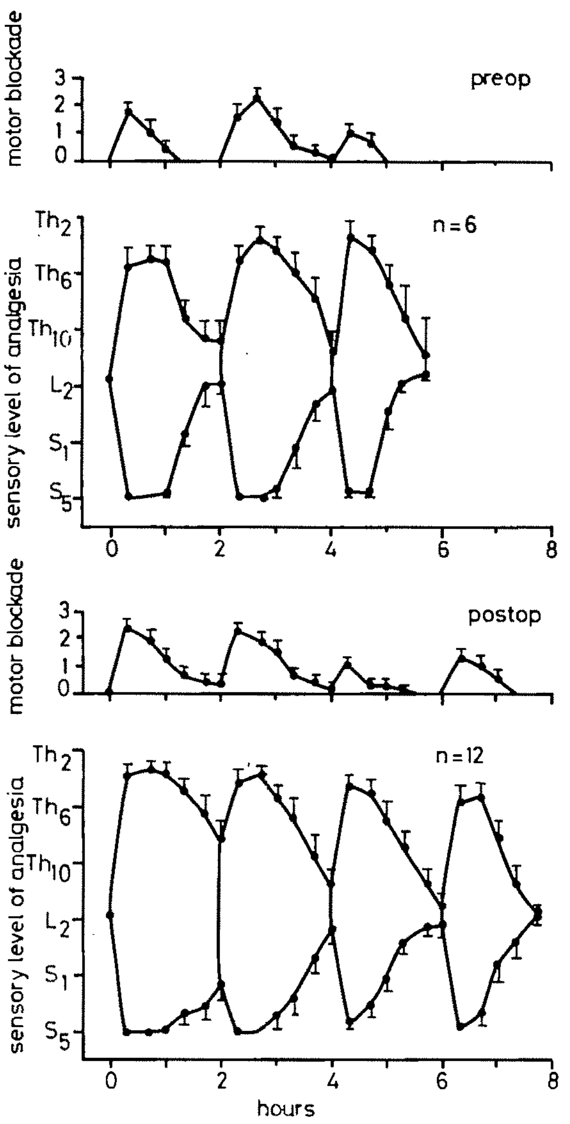


Figure 1. Levels of sensory analgesia and motor blockade (Bromage scale [6]) resulting from three 20-mL injections of epidural 2% lidocaine before surgery in patients scheduled for minor surgery (upper), and four 20-mL injections of epidural 2% lidocaine in patients undergoing minor surgery after the first injection (lower). Intervals between injections were 2 hr in both instances.

The spread of ^{99m}Tc-DTPA in the rostrad–caudad direction was greater than the 40-cm field of the γ camera in all patients (Figure 2). The distribution of the tracer within the field of view of the γ camera the day before operation was 28% (35–55%) mean + range in the upper third of camera field, 44% (35–55%) in the middle, and 30% (15–35%) in the lower third of the epidural space seen by the camera (Figure 2). The distribution values after establishment of operative analgesia were: 32% (20–50%), 43% (35–50%), 28% (15–35%) and postoperatively: 29% (20–35%), 45% (35–55%), 28% (20–35%) respectively. In all patients the rostrad spread of ^{99m}Tc-DTPA was more extensive than sensory analgesia assessed by pinprick.

In the six patients from part 2 residual lidocaine left over from the previous two injections was present in plasma immediately before the third injection of lidocaine (Figure 3) and, therefore, plasma levels of lidocaine were significantly higher after the third injection than they were after the first injection. However, there was no significant difference in the elimination of lidocaine from the epidural space as measured by the slope of the plasma concentration curves (Figure 3) after the first and third injections of lidocaine. The increase in plasma lidocaine was 0.5 ± 0.1 $\mu g \cdot ml^{-1} \cdot min^{-1}$ during the first injection and 0.3 ± 0.04 $\mu g \cdot ml^{-1} \cdot min^{-1}$ during the third injection.

Discussion

In the present study we have demonstrated that, during repeated identical doses of 2% lidocaine epidurally, there was a continuous decrease in duration of sensory analgesia, confirming earlier results (3). There was no difference in duration of analgesia between patients investigated before or after a minor surgical trauma.

The mechanism of acute tolerance, "tachyphylaxis," to local anesthetics during long-term epidural administration has not been explained although several hypotheses have been proposed (5). One proposed mechanism is that there is increased systemic uptake of the local anesthetic from the injection site owing to an increase in epidural blood flow after epidural injection of local anesthetics (7). Another proposed mechanism is that the amount of drug reaching the site of action in nerve tissues decreases with repeated injections (8).

One way to investigate the clearance and distribution of lidocaine in the epidural space, which may depend on both blood flow and diffusion within the epidural space, would be to use radioactive lidocaine. This, even if available, would present ethical problems, so we chose a tracer with nearly the same molecular weight as lidocaine (^{99m}Tc-DTPA) (9) to measure distribution in the epidural space.

The interpretation of the serum levels of lidocaine assumed to reflect elimination from the epidural space may be difficult since the actual concentration depends on both uptake from the epidural space, distribution in the plasma and tissues, and clearance in the liver. Tucker and Mather (10) have shown that the systemic absorption rate can be used as an indirect method of assessing the uptake of local anesthetics from the epidural space if the following assumptions are made:

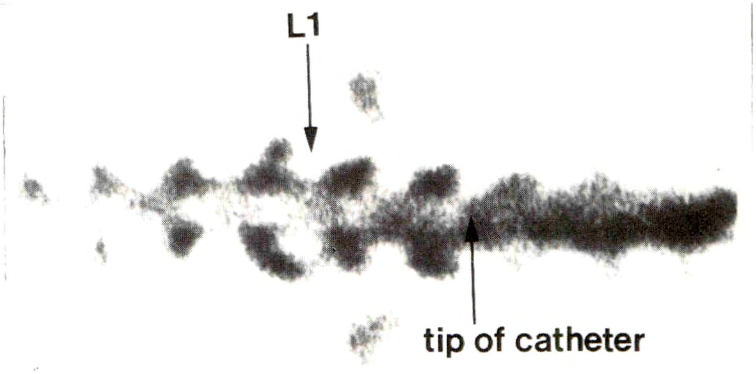


Figure 2. Distribution of ^{99m}Tc-DTPA injected epidurally at L-2 to L-3.

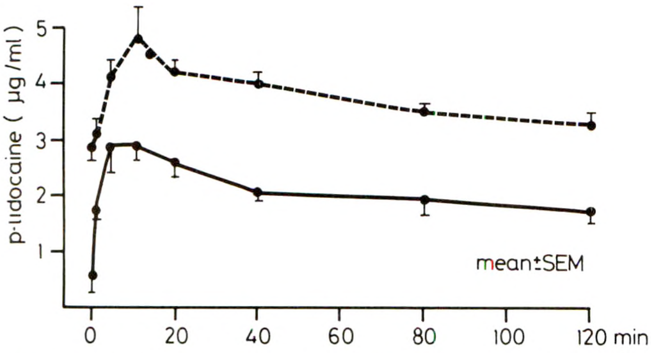


Figure 3. Serum concentrations of lidocaine after the first (**solid line**) and third (**dashed line**) injections of lidocaine 2% (3 + 17 mL) at 2-hr intervals. (The higher level of the curve before and after the third injection is due to the previously injected lidocaine.)

1. The agent is not metabolized in the epidural space.
2. Drug disposition kinetics are independent of dose, route, and rate of systemic drug input.

However our results, showing an increase in plasma lidocaine of 0.5 ± 0.1 $\mu g \cdot ml^{-1} \cdot min^{-1}$ before tachyphylaxis and 0.3 ± 0.04 $\mu g \cdot ml^{-1} \cdot min^{-1}$ during tachyphylaxis, argue strongly against tachyphylaxis to be caused by increased elimination of lidocaine from the epidural space.

In the classical study by Bromage et al. (3), there was both a decrease in duration of sensory analgesia and in the number of segments blocked, as clearly demonstrated in one patient who received repeated doses of 7.5 mL of 2% lidocaine. In our study with similar, controlled injections of lidocaine in all patients, we found the upper level of sensory analgesia of 20 and 40 min to be similar after all the injections. Furthermore, we found no evidence of an altered distribution of lidocaine during repeated injections, as assessed by ^{99m}Tc-DTPA. We have no explanation to this discrepancy between our results and those of Bromage et al. (3).

In a previous study we demonstrated that surgical trauma may enhance regression of analgesia during continuous epidural infusion of 0.5% bupivacaine since regression of the level of analgesia was significantly less in patients with chronic nonsurgical pain than it was in postoperative patients (11). This is in contrast to the present study in which there was no difference in spread of lidocaine vs ^{99m}Tc-DTPA between patients studied before and after surgery. Perhaps the surgical trauma in this study was minimal compared with that associated with intraabdominal procedures studied in previous reports (1,7,11).

Local anesthetics in concentrations (i.e., 2% lidocaine) as seen during clinical use may cause localized edema in the nerves (12) and thereby hinder intraneuronal diffusion of the drug, thus promoting tachyphylaxis. However, in isolated nerve preparations bupivacaine does not produce tachyphylaxis (13), though the study time in vitro (4 hr) with this long-acting drug was too short to allow correlation to clinical tachyphylaxis.

In conclusion, our results confirm that tachyphylaxis occurs during repeated epidural injections of 2% lidocaine. Tachyphylaxis could not be explained by increased clearance or altered distribution of lidocaine. The pathogenesis of tachyphylaxis remains unknown but factors including edema of the nerve, down-regulation of local anesthetic receptors in nerve tissue, or changes in afferent activity or spinal inhibition of the afferent nervous traffic (5) must be considered in future studies.

References

1. Mogensen T, Hjortsø NC, Bigler D, Lund C, Kehlet H. The unpredictability of regression of analgesia during continuous postoperative infusion of bupivacaine. Br J Anaesth 1988; 60:515–9.
2. Renck H, Edstrøm H, Kinneberger B, Brant G. Thoracic epidural analgesia: II. Prolongation in the early postoperative period by continuous injection of 1% bupivacaine. Acta Anaesthesiol Scand 1976;20:47–56.
3. Bromage PR, Pettigrew RT, Corwell DE. Tachyphylaxis in epidural analgesia: 1. Augmentation and decay of local anesthesia. J Clin Pharmacol 1969;9:30–8.

4. Mather LE. Tachyphylaxis in regional anaesthesia: can we reconcile clinical observation and laboratory measurements? Anaesthesiol Intensivmedizin 1986;176:3–9.
5. Bigler D, Lund C, Mogensen T, Hjortsø NC, Kehlet H. Tachyphylaxis during postoperative epidural analgesia—new insights. Acta Anaesthesiol Scand 1987;31:664–5.
6. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand (Suppl XVI) 1965;16:55–69.
7. Mogensen T, Højgaard L, Scott NB, Henriksen JH, Kehlet H. Epidural blood flow and regression of sensory analgesia during continuous postoperative epidural bupivacaine infusion. Anesth Analg 1988;67:809–13.
8. Raj PP, Denson DD, De Jong RH. No tachyphylaxis with prolonged, continuous bupivacaine. Anaesthesiol Intensivmedizin 1986;176:10–8.
9. Heidenrich P, Kriegel H, Hör, Göger H, Keyl W, Schramm E. ^{99m}Tc-DTPA (Sn): Biologisher und klinische Untersuchungen zur Verteilung, Kinetik und In-vivo-Stabilität einer neuen Clearance-Substanz. Strahlentherapie 1975;74:174–85.
10. Tucker GT, Mather L. Pharmacology of local anaesthetic agents. Br J Anaesth 1975;47:213–24.
11. Mogensen T, Scott NB, Lund C, Bigler D, Hjortsø NC, Kehlet H. The role of acute and chronic pain in regression of sensory analgesia during continuous epidural bupivacaine infusion. Anesth Analg 1988;67:737–40.
12. Myers RR, Kalichman MW, Reisner LS, Powell H. Neurotoxicity of local anesthetics: altered perineural permeability, edema and nerve fiber injury. Anesthesiology 1986;64:29–35.
13. Lipfert P, Holthusen H, Arndt JO. Tachyphylaxis to local anesthetics does not result from reduced drug effectiveness at the nerve itself. Anesthesiology 1989;70:721–5.

ANESTH ANALG
1989;69:185–91

Intrathecal Clonidine Suppresses Noxiously Evoked Activity of Spinal Wide Dynamic Range Neurons in Cats

Kenji Murata, MD, Itsuo Nakagawa, MD, Yukihiro Kumeta, MD,
Luke M. Kitahata, MD, PhD, and J. G. Collins, PhD

MURATA K, NAKAGAWA I, KUMETA Y, KITAHATA LM, COLLINS JG. Intrathecal clonidine suppresses noxiously evoked activity of spinal wide dynamic range neurons in cats. Anesth Analg 1989;69:185–91.

The analgesic effectiveness of perispinal clonidine administration prompted us to evaluate clonidine effects on spinal dorsal horn wide dynamic range neurons. Intrathecal clonidine produced a dose-dependent (10 and 30 μg), yohimbine-reversible suppression of noxiously evoked activity in decerebrate, spinal cord-transected cats. In addition, combining ineffective intrathecal doses of morphine (25 μg) and clonidine (5 μg) produced statistically significant, reversible suppression of noxiously evoked activity. The time course of suppression was similar to that observed behaviorally. These results support the role of spinal α_2-adrenergic receptors in clonidine analgesia.

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—clonidine. SPINAL CORD—clonidine effects.

Clonidine, a clinically useful antihypertensive agent, is effective in blocking noxious stimuli when administered systemically, epidurally, intracerebroventricularly, or intrathecally in many animal species as determined by various analgesiometric methods—tail-flick, hot plate, writhing (1–12). In addition, several clinical reports have documented the analgesic efficacy of clonidine in humans (13–18) and its ability to reduce general anesthetic requirements (19–21). These observations lead to the proposal that clonidine may have an analgesic action in addition to its established, centrally mediated antihypertensive effect.

Our current understanding of the neurophysiology and pharmacology of pain transmission indicates that both spinal and supraspinal sites are likely to be involved in the analgesic actions of clonidine. Previously, our laboratory evaluated opioid and adrenergic agonist effects on spinal processing of nociceptive information (22–25). Because of the reported perispinal use of clonidine for analgesia in humans and behavioral evidence of its analgesic effectiveness in animals, we were anxious to evaluate, using a sensitive neurophysiologic assay, the effects of clonidine on noxiously evoked activity of spinal dorsal horn, wide dynamic range (WDR) neurons. WDR neurons are thought to be important for the signaling of pain, have been shown to be readily suppressed by analgesic drugs, and are known to be associated with information transmission in the spinothalamic tract. We were particularly interested in examining the receptor selectivity of the drug and its duration of action after spinal administration as well as possible additive effects associated with morphine-clonidine combinations. Some of these results have appeared in abstract form (26).

Methods

Extracellular, single-unit recordings were obtained from the lumbar dorsal horn in decerebrate, spinal cord-transected cats. Forty-seven cats of either sex, weighing 3.2–4.7 kg, were used. Only one neuron with one dose of drug was studied in each animal to avoid cumulative effects of the drugs. All appropriate guidelines for the humane care and use of animals were followed in this study which was approved by the Yale Animal Care and Use Committee.

This work was supported by grant NS-09871 from the National Institutes of Health.

Received from the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication March 13, 1989.

Address correspondence to Dr. Collins, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

©1989 by the International Anesthesia Research Society

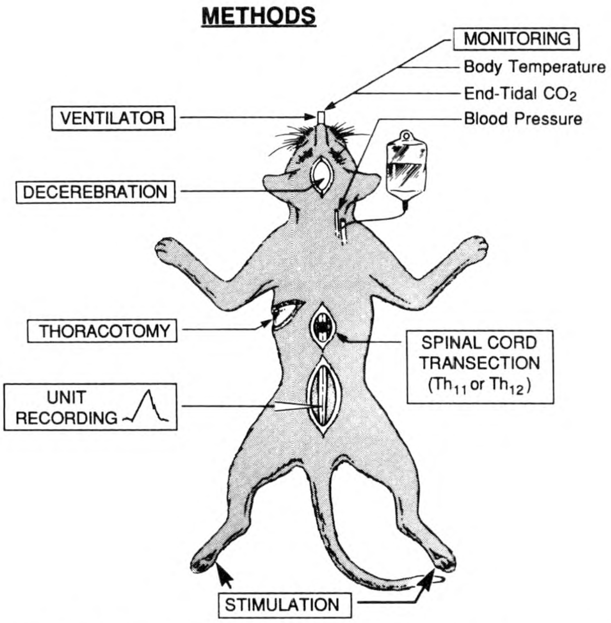


Figure 1. Schematic representation of the experimental preparation. The spinal cord was transected at T-11 or T-12 and a laminectomy was performed from L-4 through L-6. A thoracotomy was performed to avoid movement of the spinal cord due to mechanical ventilation.

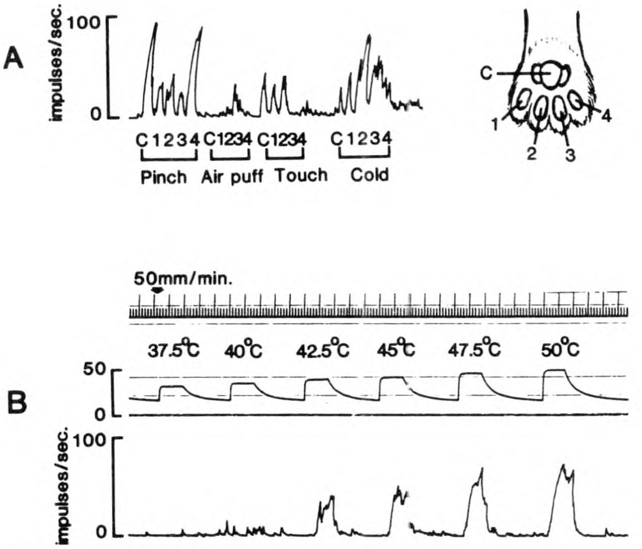


Figure 2. An example of a response profile of a WDR neuron. **A,** WDR neuronal responses to various stimuli are shown. Numbers and C indicate the site of stimulation on the foot. As typically seen with WDR neurons, the response increases with increasing intensity of stimulation. **B,** Neuronal responses to increasing intensity of radiant heat. The response became greater as the temperature was increased.

Surgical preparation was carried out under general anesthesia (halothane-nitrous oxide-oxygen). See Figure 1 for a summary of animal preparation. After the placement of both an external jugular vein catheter for fluid and drug administration and monitoring of central venous pressure, as well as a carotid artery catheter for monitoring blood pressure, the trachea was intubated and the animals mechanically ventilated while paralyzed with pancuronium bromide (0.1–0.15 $mg \cdot kg^{-1} \cdot h^{-1}$). End-tidal CO_2 was monitored and maintained between 3.0% and 4.0%. Esophageal temperature was maintained between 37 and 38°C by servocontrolled heating lamps.

After instrumentation, the cats were decerebrated by electrolytic lesions in the midbrain reticular formation and the spinal cord was transected at T-11 or T-12. (Spinal cord transection allowed us to monitor drug effects on the dorsal horn of the spinal cord in the absence of descending supraspinal influences.) After decerebration, anesthesia was discontinued and the animals were ventilated with room air. This preparation provided animals that were pain-free during both surgery and neurophysiologic recordings, and yet permitted us to study the effects of drugs in a preparation that was drug-free except for the neuromuscular blocking agent.

A laminectomy was performed at L-4 to L-6, the duramater was cut and reflected, and the arachnoid removed at the site of microelectrode placement. A thoracotomy was performed to reduce spinal cord movement due to ventilation. A minimum of 2 h elapsed between spinal cord transection and the beginning of neuronal recording.

While searching for individual neurons, the spinal cord was bathed with 37°C physiologic saline. Tungsten microelectrodes were advanced into the lumbar enlargement of the dorsal horn of the spinal cord while receptive fields on the ipsilateral hind paw were stimulated. When activity of a single neuron was isolated, the cell type was identified by its response profile to peripheral stimuli as shown in Figure 2. If the response profile indicated a WDR neuron (increasing response to increasing stimulus intensity with maximum response elicited by noxious stimulation), baseline studies were performed in which both spontaneous and noxiously evoked activity were recorded. Spontaneous activity was averaged for 30 sec before stimulus presentation. Noxiously evoked activity was produced by applying a 51°C radiant heat stimulus for 8 sec to the receptive field on the hind paw. After baseline studies, the saline that had been bathing the spinal cord was carefully removed by gentle suctioning and replaced by 0.5 mL of 37°C physiologic saline that contained drug without preservatives. The applied drugs were 10 (N = 8) and 30 (N = 15) μg of clonidine, 25 (N = 8) μg morphine, and 5 μg of clonidine combined with 25 μg of morphine (N = 8). In nine experiments, 30 min after administering 30 μg of clonidine, a maximum dose of 1.5 mg/kg of yohimbine (α_2 antagonist)

Table 1. Mean Suppressive Effects of Intrathecally Administered Clonidine on Dorsal Horn Wide Dynamic Range Neuronal Activity

Dose of Clonidine	Baseline	15 min	30 min
5 μg	N = 8	N = 8	N = 8
Spontaneous activity (impulses/sec)	4.4 ± 1.7	2.6 ± 1.7 (73%)	4.4 ± 1.7 (103%)
Evoked activity (impulses/sec)	51.6 ± 9.4	47.8 ± 9.8 (90%)	56.6 ± 10.0 (98%)
10 μg	N = 8	N = 8	N = 7
Spontaneous activity (impulses/sec)	16.8 ± 6.1	9.2 ± 4.5 (66%)	9.3 ± 5.1 (60%)
Evoked activity (impulses/sec)	60.3 ± 12.6	43.2 ± 7.8* (74%)	38. ± 9.2* (65%)
30 μg	N = 14	N = 14	N = 13
Spontaneous activity (impulses/sec)	8.8 ± 2.7	4.3 ± 2.1* (23%)	3.3 ± 1.7* (19%)
Evoked activity (impulses/sec)	53.3 ± 9.1	32.4 ± 8.3* (52%)	25.5 ± 6.6* (39%)

All values given are mean ± SE. Numbers in parentheses indicate percentage of baseline values.
*$P < 0.05$, significantly different from baseline.

was administered intravenously to test for reversal of the effects of clonidine. In six experiments after the administration of 30 μg of clonidine, observations continued for several hours to estimate the effective duration of action of clonidine. In five of those experiments the physiologic saline that contained the drug was not removed from the spinal cord surface (i.e., duration of action of the total administered dose was determined). In one experiment, the drug containing saline was removed 1 h after its administration and replaced with drug-free saline. In all instances the spinal cord was monitored microscopically to insure that it did not dry out. Additional small volumes of drug-free saline were placed on the spinal cord as necessary.

In six experiments in which 30 μg of clonidine was used, in addition to mean blood pressure, which in all cases was monitored continuously until the experiments were finished, central venous pressure (CVP) was measured every 15 min for periods of up to 2 h to evaluate the cardiovascular effects of intrathecally administered clonidine. In most experiments in which 10 μg of clonidine was used, neuronal activity was recorded for longer periods in an attempt to measure spontaneous recovery after spinal clonidine administration.

To study the effects of combined morphine and clonidine we first compared the effect of 5 μg of clonidine or 25 μg of morphine given separately with the effect of the two combined. The 25-μg morphine dose was determined from previous dose–response studies (24). In three experiments, 30 min after administering the morphine-clonidine combination, reversal was attempted with a yohimbine-naloxone combination. A maximum dose of yohimbine 1.5 mg/kg IV was slowly administered. For some cells reversal was attempted at later time points.

All data were collected on-line with a digital computer (DEC PDP 11/40, Digital Equipment Corp, Marlboro, MA) for subsequent off-line analysis. Student's *t*-test for paired and unpaired data were used to assess statistical significance. Differences were considered to be significant if P values were <0.05.

Results

All the neurons included in this study (N = 47) were of the WDR type.

Effects of the Intrathecal Clonidine on Spontaneous and Evoked Activity of WDR Neurons

Table 1 shows the effects of intrathecally administered clonidine on the mean spontaneous and evoked activity of the WDR neurons. The 5-μg dose did not produce a statistically significant reduction in spontaneous or evoked activity either 15 or 30 min after drug administration. The 10-μg dose yielded a statistically significant suppression of only the evoked activity at 15 and 30 min. The 30-μg dose produced significant reductions in both types of activity at both 15 and 30 min.

Figure 3 depicts the dose-dependent clonidine

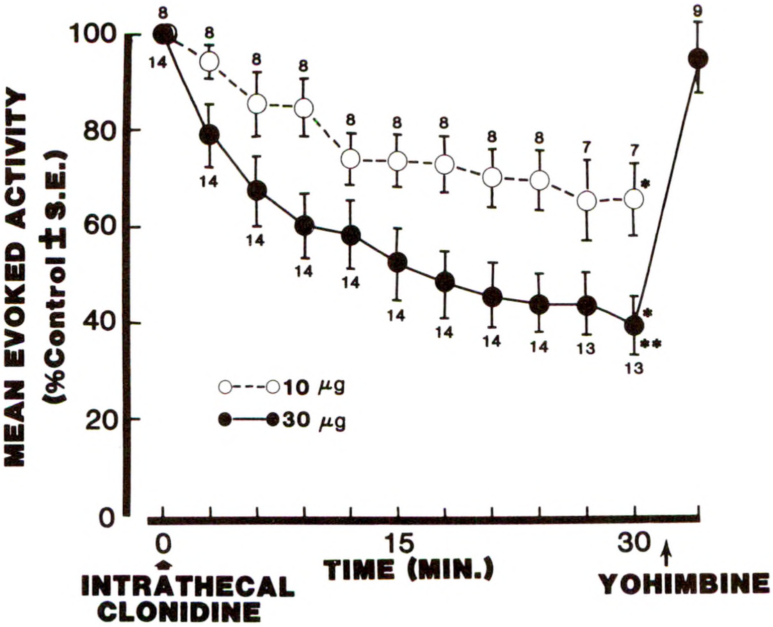


Figure 3. Effects of two doses of intrathecal clonidine on the mean evoked activity of WDR neurons. Both 10 and 30 µg of clonidine produced statistically significant reduction of evoked activity of WDR neurons. The suppression by 30 µg of clonidine was reversed by systemic yohimbine (0.5–1.5 mg/kg). Each point represents the mean ± SE. *Significantly different from baseline. **Significantly different from 10 µg clonidine at 30 min.

depression of mean evoked activity of all cells studied as well as the reversal of that depression by yohimbine (selective α_2 antagonist, 0.5–1.5 mg/kg administered intravenously).

Duration of Action after Intrathecally Administered Clonidine

Figure 4 indicates the duration of action, defined as suppression >20%, in four neurons after intrathecally administered clonidine. In the two neurons shown in Figure 4, *A* and *B*, suppression was observed for 5 and 6 h, respectively. In both cases, the suppression, lasting for that time, was reversed by the systemic administration of yohimbine. In Figure 4*C* we see that 10 µg of clonidine produced suppression that recovered spontaneously to within 20% of control at 4 h and 30 min. An additional neuron (Figure 4*D*) was studied after 10 µg of spinally administered clonidine, and, in spite of the fact that the drug containing saline was removed and replaced by drug-free saline 1 h after its administration, the noxiously evoked activity of the WDR neuron remained suppressed for 3 h and 30 min.

Cardiovascular Effects of Intrathecal Clonidine

Spinally administered clonidine (30 µg) did not change mean blood pressure or central venous pressure in the decerebrate, spinal cord-transected cat during the 2-h period of observation.

Effect of the Combined 5 µg of Clonidine and 25 µg of Morphine

As seen in Figure 5, in spite of the fact that 5 µg of clonidine alone or 25 µg of morphine alone did not produce significant neuronal depression within 30 min, when used in combination there was a significant suppression of mean evoked activity of the WDR neurons studied. In the three cases in which it was tested, the suppression was reversed by systemic injection of a combination of yohimbine (0.5–1.5 mg/kg) and naloxone (0.1 mg). In two neurons, after combined 5 µg of clonidine and 25 µg of morphine, neuronal activity was observed for 2 and 3 h, respectively. In both instances, the suppression was reversed to 97% and 40% of control by the systemic administration of yohimbine and naloxone, respectively.

Discussion

Site of Action of Clonidine Analgesia

In this study using a spinally transected cat model, intrathecally administered clonidine produced a dose-dependent reduction of noxiously evoked activity of WDR neurons in the spinal dorsal horn. These data demonstrate that a site of action for clonidine modulation of pain transmission is independent of supraspinal influences and likely to be within the spinal cord. These results do not eliminate the possibility of a more peripheral site of action being involved as well.

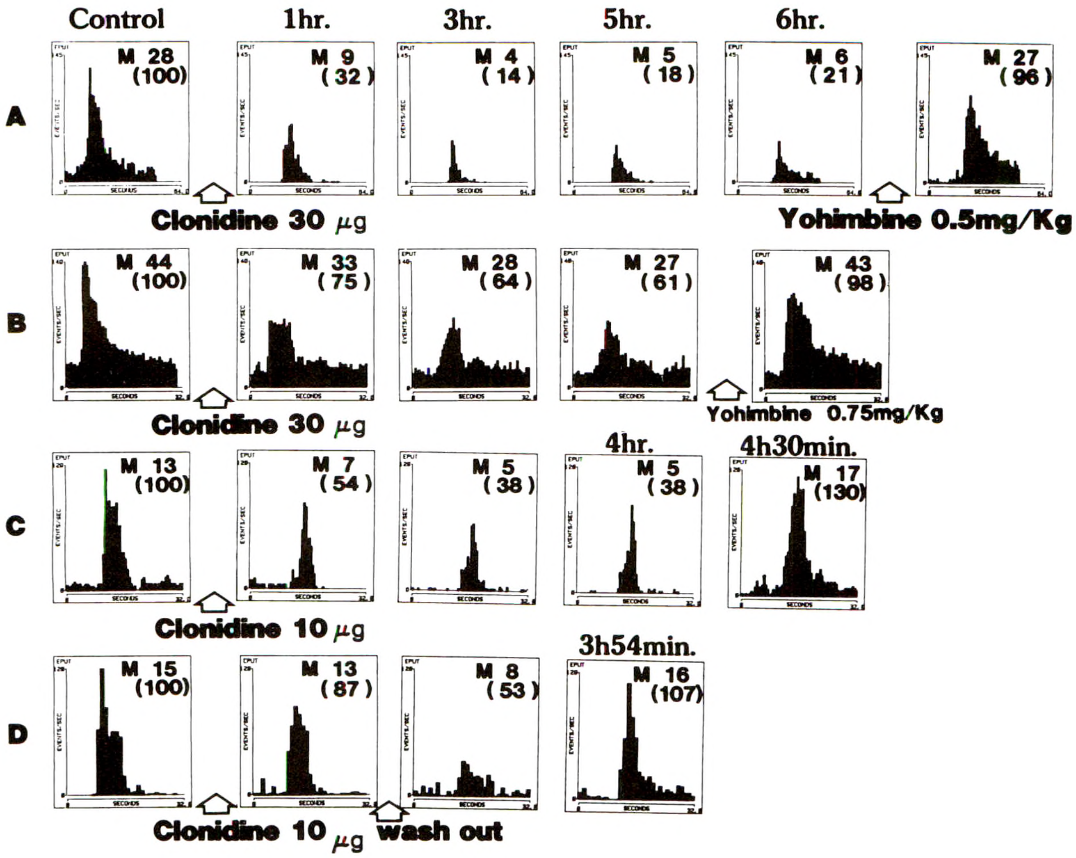


Figure 4. This figure indicates the long-lasting antinociceptive effect of clonidine on evoked activity of four WDR neurons (**A–C**). The numbers following letter *M* in each square indicate the mean evoked activity during stimulation. The numbers in parentheses indicate percent of baseline values. **D,** Even with removal of the drug containing saline from the surface of the spinal cord immediately after the 1-h time point the suppression was still long-lasting.

These findings support those of other investigators who suggest a pure spinal cord-elicited analgesia after clonidine administration (27,28,29).

Receptor Selectivity of Clonidine

The receptor selectivity of the analgesic effects of clonidine was unclear in earlier reports (30,31), whereas recently most studies have shown that antinociceptive effects of clonidine are reversed by selective α_2 antagonists but unaltered by α_1-adrenergic receptor blocking agents (32–35).

The present study shows that clonidine-induced reduction of noxiously evoked activity on WDR neurons is reversed by the selective α_2 antagonist, yohimbine. These results suggest that the α_2-adrenergic receptors in the spinal cord may play an important role in the spinal processing of nociceptive information.

Duration of Action of Neuronal Suppression by Intrathecal Clonidine

The present data show that intrathecal clonidine produced a long-acting yohimbine-reversible reduction in activity of WDR neurons and are in agreement with clinical reports of long-lasting analgesia after intrathecal clonidine (16,18). Coombs et al. demonstrated that a 0.3-mg intrathecal clonidine bolus provided more than 18 h of analgesia in a 52-yr-old woman with cancer pain (16). In addition, the same dose and route of clonidine yielded 7 h of almost complete pain relief in a 49-yr-old woman with intractable cancer pain (18). The same authors also stated that histological examination of the spinal cord revealed no apparent demyelination or gliosis of the posterior columns and that neurons of the anterior horns were intact; no vacuolation or central chromatolysis was observed (18).

On the basis of these observations, the use of perispinal clonidine for analgesia would be expected to be useful for relief of chronic pain.

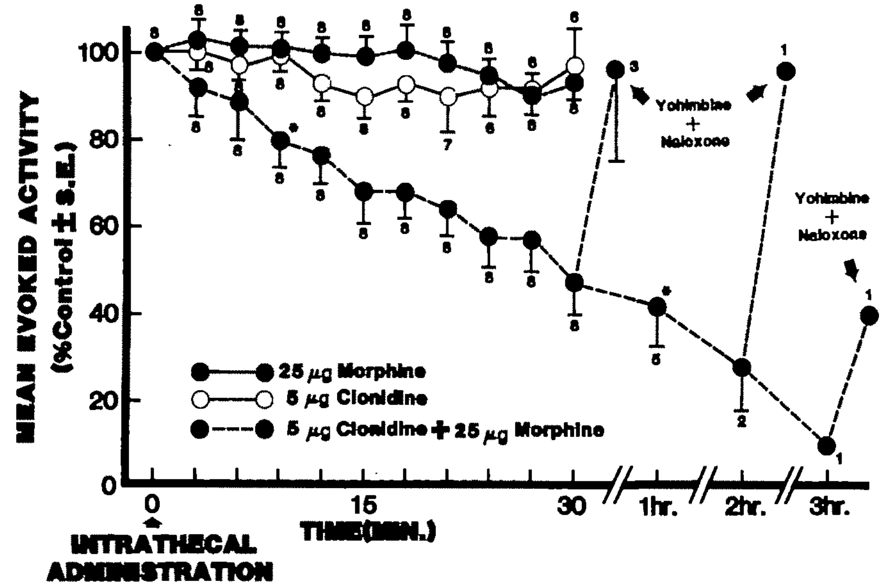


Figure 5. Effects of 5 μg of clonidine and 25 μg of morphine separately and the combination of 5 μg of clonidine and 25 μg of morphine on the mean evoked activity of WDR neurons. Neither low-dose clonidine nor morphine produced a discernible alteration in activity. Combined application produced a statistically significant reduction of evoked activity of WDR neurons within 9 min of administration. The suppression was reversed by systemic injections of naloxone (0.1 mg) and yohimbine (0.5–1.5 mg/kg). Each point represents the mean ± SE. Numbers by each SE bar indicate the number of neurons at each point. *Significantly different from baseline values.

Effect on the Cardiovascular System of Intrathecal Clonidine

Because of the relatively high dose of clonidine employed in this study (30 μg), systolic blood pressure and central venous pressure were monitored for 2 h after drug administration with no noticeable change in either parameter. This is in contrast to clinical reports that intrathecal clonidine caused hypotension or bradycardia (16,18). Yasuoka and Yaksh (36) reported that intrathecal clonidine produced hypotension in cats but Eisenach et al. (10) reported that epidural clonidine did not produce hypotension in sheep. Of importance to this study, since clonidine-induced changes in cardiovascular parameters were not observed, it is unlikely that they were the reason for the depression of neuronal activity.

Combined Effect of Low-Dose Clonidine and Morphine

Despite the fact that low doses of both clonidine and morphine did not reduce WDR neuronal activity, the combination of the two produced significant neuronal suppression. This observation is in keeping with that of clinical reports by Coombs et al. (16,18) and animal studies by Yaksh and Reddy (12). The multiplicative effect seen in this preparation was clearly not dependent upon supraspinal influences, and therefore, we may assume that the interactions were occurring at the spinal level.

References

1. Paalzow I. Analgesia produced by clonidine in mice and rats. J Pharm Pharmacol 1974;26:361–3.
2. Fielding S, Wilker J, Hynes M, Szewczack M, Novick WJ, Lal H. A comparison of clonidine with morphine for antinociceptive and antiwithdrawal actions. J Pharmacol Exp Ther 1978; 207:899–905.
3. Skingle M, Hayes AG, Tyers MB. Antinociceptive activity of clonidine in the mouse, rat and dog. Life Sci 1982;31:1123–32.
4. Paalzow GHM, Paalzow LK. Separate noradrenergic receptors could mediate clonidine-induced antinociception. J Pharmacol Exp Ther 1982;223:795–800.
5. Paalzow G, Paalzow L. Clonidine antinociceptive activity: effects of drugs influencing central monoaminergic and cholinergic mechanisms in the rat. Nauyn-Schmiedeberg's Arch Pharmacol 1976;292:119–26.
6. Spaulding TC, Fielding S, Venafro JJ, Lal H. Antinociceptive activity of clonidine and its potentiation of morphine analgesia. Eur J Pharmacol 1979;58:19–25.
7. Takahashi M, Izumi R, Kaneto H. The role of the catecholaminergic mechanism in foot shock (FS) stress and immobilized-water immersion (IW) stress-induced analgesia in mice. Jpn J Pharmacol 1984;35:175–9.
8. Reddy SVR, Maderdrut JL, Yaksh TL. Spinal cord pharmacology of adrenergic agonist-mediated antinociception. J Pharmacol Exp Ther 1980;213:525–33.
9. Milne B, Cervenko FW, Jhamandas K, Sutak M. Intrathecal clonidine: analgesia and effect on opiate withdrawal in the rat. Anesthesiology 1985;62:384–9.
10. Eisenach JC, Dewan DM, Rose JC, Angelo JM. Epidural clonidine produces antinociception, but not hypotension, in sheep. Anesthesiology 1987;66:496–501.
11. Post C, Gordh T, Minor BG, Archer T, Freedman J. Antinociceptive effects and spinal cord tissue concentrations after intrathecal injection of guanfacine or clonidine into rats. Anesth Analg 1987;66:317–24.
12. Yaksh TL, Reddy SVR. Studies in the primate on the analgesic effects associated with intrathecal actions of opiates, α-adrenergic agonists and baclofen. Anesthesiology 1981; 54:451–67.
13. Bakris GL, Cross PD, Hammerstan JE. The use of clonidine for management of opiate abstinence in a chronic pain patient. Mayo Clin Proc 1982;57:657–60.
14. Goldstein JA. Clonidine as analgesic. Biol Psychiatry 1983; 18:1339–40.
15. Gordh TE, Tamsen A. A study on the analgesic effect of clonidine in man. Acta Anesthesiol Scand 1983;78(suppl):72.

16. Coombs DW, Saunders RL, Lachance D, Savage S, Ragnarsson TS, Jensen LE. Intrathecal morphine tolerance: use of intrathecal clonidine, DADLE, and intraventricular morphine. Anesthesiology 1985;62:358–63.
17. Tamsen A, Gordh T. Epidural clonidine produces analgesia. Lancet 1984;28:231–2.
18. Coombs DW, Saunders RL, Fratkin JD, Jensen LE, Murphy CA. Continuous intrathecal hydromorphone and clonidine for intractable cancer pain. J Neurosurg 1986;64:890–4.
19. Kaukinen S, Pyykko K. The potentiation of halothane anaesthesia by clonidine. Acta Anaesthesiol Scand 1979;23:107–11.
20. Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesth Analg 1982;61:741–5.
21. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 1986;64:36–42.
22. Kitahata LM, Kosaka Y, Taub A, Bonikos K, Hoffert M. Lamina-specific suppression of dorsal-horn unit activity by morphine sulfate. Anesthesiology 1974;41:39–48.
23. Suzukawa M, Matsumoto M, Collins JG, Kitahata LM, Yuge O. Dose-response suppression of noxiously evoked activity of WDR neurons by spinally administered fentanyl. Anesthesiology 1983;58:510–3.
24. Homma E, Collins JG, Kitahata LM, Matsumoto M, Kawahara M. Suppression of noxiously evoked WDR dorsal horn neuronal activity by spinally administered morphine. Anesthesiology 1983;58:232–6.
25. Collins JG, Kitahata LM, Matsumoto M, Homma E, Suzukawa M. Spinally administered epinephrine suppresses noxiously evoked activity of WDR neurons in the dorsal horn of spinal cord. Anesthesiology 1984;60:269–75.
26. Nakagawa I, Kitahata LM, Murata K, Omote K, Collins JG. Spinal mechanism of clonidine analgesia and its synergism with morphine [abstract]. Anesth Analg 1988;67:157.
27. Spaulding TC, Venafro JJ, Ma MG, Fielding S. The dissociation of the antinociceptive effect of clonidine from supraspinal structures. Neuropharmacology 1979;18:103–5.
28. Kawasaki K, Takesue H, Matsushita A. Modulation of spinal reflex activities in acute spinal rats with alpha adrenergic agonists and antagonists. Jpn J Pharmacol 1978;28:165–8.
29. Calvillo O, Ghignone M. Primary afferent depolarization of cutaneous C fibers in the cat spinal cord evoked by clonidine. Fed Proc 1985;44:890–9.
30. Anden NE, Grabowska M, Strombom U. Different alpha-adrenoreceptors in the central nervous system mediating biochemical and functional effects of clonidine and receptor blocking agents. Naunyn-Schmiedeberg's Arch Pharmacol 1976; 292:43–52.
31. Cedarbaum JM, Aghajanian GK. Catecholamine receptors on locus corruleus neurons: pharmacological characterization. Eur J Pharmacol 1977;44:375–85.
32. Howe JR, Wang JY, Yaksh TL. Selective antagonism of the antinociceptive effect of intrathecally applied alpha-adrenergic agonists by intrathecal prazosin and intrathecal yohimbine. J Pharmacol Exp Ther 1983;224:552–8.
33. Davies J, Johnston SE, Hill DR, Quinlan JE. Tizanidine (DS103-282), a centrally acting muscle relaxant, selectively depresses excitation of feline dorsal horn neurons to noxious peripheral stimuli by an action at alpha-adrenoceptors. Neurosci Lett 1984;48:197–202.
34. Davis J, Quinlan JE. Selective inhibition of responses of feline dorsal horn neurons to noxious cutaneous stimuli by tizanidine (DS103-282) and noradrenaline: involvement of alpha-adrenoceptors. Neuroscience 1985;16:673–82.
35. Bently GA, Newton SH, Starr J. Studies on the antinociceptive action of α-agonist drugs and their interactions with opioid mechanisms. Br J Pharmacol 1983;79:125–34.
36. Yasuoka S, Yaksh TL. Effects on nociceptive threshold and blood pressure of intrathecally administered morphine and alpha-adrenergic agonists. Neuropharmacology 1983;22:309–15.

1989;69:192–6

Intraoperative Temperature Monitoring Sites in Infants and Children and the Effect of Inspired Gas Warming on Esophageal Temperature

Bruno Bissonnette, MD, Daniel I. Sessler, MD, and Pierre LaFlamme, MD

BISSONNETTE B, SESSLER DI, LAFLAMME P. Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature. Anesth Analg 1989;69:192–6.

This study tested the hypotheses that 1) temperatures of "central" sites are similar in infants and children undergoing noncardiac surgery and 2) airway heating and humidification increases distal esophageal temperature. Twenty children were randomly assigned to receive 1) active airway humidification using an airway heater and humidifier set at 37°C (N = 8), 2) passive airway humidification using a heat and moisture exchanger (N = 6), or 3) no airway humidification and/or heating (control, N = 6). There were no statistically significant differences between tympanic membrane, esophageal, rectal, and axillary temperatures. The temperatures of the peripheral skin surface (forearm and fingertip) were significantly lower than tympanic membrane temperature and significantly different from each other. Although esophageal and tympanic membrane temperatures in the entire group were similar, esophageal temperatures in patients receiving active and passive airway humidification were about 0.35°C above tympanic temperatures after induction of anesthesia. In contrast, esophageal temperatures in patients without airway humidification were 0.25°C below tympanic temperatures after induction of anesthesia. Esophageal–tympanic membrane temperature differences in the patients given active and passive humidification differed significantly from the corresponding sum in the control group at all times, but not from each other.

Key Words: ANESTHESIA—pediatric. TEMPERATURE, BODY—measurement sites. MEASUREMENT TECHNIQUES—body temperature.

Intraoperative measurements of body temperature help detect hypothermia and malignant hyperthermia. Accurate determination of body temperature also helps determine the efficacy of various warming techniques (e.g., warming blankets, fluid warmers, and airway humidification) and helps evaluate the thermoregulatory effects of different anesthetic drugs. Comparison between different thermoregulatory studies in children is difficult because it is not known to what extent various temperatures are comparable. Previous studies have indicated that tympanic membrane, esophageal, and rectal temperatures are similar in anesthetized adults undergoing noncardiac surgery (1). We tested the hypothesis that axillary temperatures are also "central" (e.g., similar to tympanic membrane, esophageal, and rectal temperatures) in infants and children undergoing noncardiac surgery and compared these central temperatures with two peripheral skin surface measurements (forearm and fingertip).

Elimination of metabolic heat by respiratory gases can decrease *upper* esophageal temperature by about 1°C (2); active airway heating is likely to increase this temperature in a similar fashion. The temperature in the *lower* (retrocardiac) portion of the esophagus is generally assumed to be influenced minimally by the temperature of respiratory gases. Because infants and children have minimal thermal insulation between the tracheobronchial tree and the esophagus, the effects of respiratory gas temperature on esophageal temperature are likely to be more pronounced in them. Accordingly, we also investigated whether

---

Supported by grants from Gibeck Respiration, Inc. and Mallinckrodt Critical Care, Mallinckrodt, Inc.

Presented in part at the annual meeting of the International Anesthesia Research Society, March, 1989.

Received from the Department of Anesthesia, Hospital for Sick Children, Toronto, Ontario, and the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication April 4, 1989.

Address correspondence to Dr. Sessler, Department of Anesthesia, Room C-450, University of California, San Francisco, CA 94143-0648.

©1989 by the International Anesthesia Research Society

airway heating and humidification would increase lower esophageal temperature in infants and children.

Materials and Methods

With approval from the Hospital for Sick Children Ethical Committee, we studied 20 unpremedicated ASA physical status 1 or 2 pediatric patients after obtaining written, informed consent from their parents. All patients were scheduled for peripheral surgery and weighed between 5 and 30 kg. None had a history of problems with the tympanic membrane, middle ear, or esophagus.

Patients were randomly assigned to one of three protocols: 1) active airway humidification and warming using a servocontrolled airway heater and humidifier (Fisher and Paykel Ltd., Auckland, New Zealand) set at 37°C (N = 8); 2) passive airway humidification using the Humid-Vent 1 (Gibeck Respiration, Inc., Schaumburg, IL), heat and moisture exchanger between the endotracheal tube connector and the Ayre's *t*-piece (N = 6); or 3) no airway humidification and heating (control, N = 6). With the designated type of humidification instituted, anesthesia was induced with halothane and 70% nitrous oxide in oxygen. The trachea of each patient was intubated without administration of muscle relaxants. Anesthesia was maintained during surgery with halothane and 70% nitrous oxide administered with a Rees modification of an Ayre's *t*-piece. Barbiturates, opiates, and muscle relaxants were not administered during surgery. Fresh gas flows were calculated using the formula of Rose and Froese (3); respiratory rate was controlled at approximately 30/min and tidal volume (about 12 mL/kg) was adjusted to maintain an end-tidal P_{CO_2} near 35 mm Hg.

Temperatures were monitored using disposable, sterile thermocouples and thermometers (model 6500, Mon-a-Therm, Inc., St. Louis, MO). The cotton-covered tympanic thermocouples were placed in contact with the tympanic membrane under direct vision using an otoscope. Esophageal probes were incorporated in 12 French stethoscopes which were positioned to obtain maximal heart sounds. Rectal probes were inserted to a depth of 5 cm and taped in place. Mon-a-Therm skin surface thermocouples (1-cm diameter disks) were placed on the radial side of the forearm midway between the elbow and the wrist and at the fingertip (on an arm without an intravenous catheter). One of these disks also was placed over the axillary artery and this arm secured in the adducted position during surgery. Temperatures were recorded every 10 min during the first 60 min of surgery. We also recorded room temperature and the patient's age and weight.

Although tympanic membrane temperatures have no greater physiological significance than rectal or esophageal temperatures, we compared values from other monitoring sites with tympanic temperature because it is the conventional standard. The temperature of each measurement site was subtracted from tympanic membrane temperature and the results from each site at each time were averaged. Differences in esophageal temperatures during each humidification protocol were determined similarly. Patient groups were compared using one-way analysis of variance and Student-Newman-Keuls tests with differences considered statistically significant when $P < 0.05$.

Results

The children's average weight was 15 ± 5.9 kg (SD), the age ranged from 6 months to 8 years (average = 4.0 ± 2.2 yr), and room temperatures ranged from 19.5 to 25.1°C (average = 22.1 ± 1.1°C). Most of the operations were hypospadious repairs and peripheral orthopedic procedures. None of the demographic characteristics, types of surgery, or room temperatures were significantly different in the three humidification groups.

Figure 1 shows the differences between the temperatures recorded at each measurement site and tympanic membrane temperature. Differences between tympanic membrane temperature and those of the other central measurement sites (esophageal, rectal, and axillary) were not significantly different at any time. In contrast, the temperatures of the peripheral skin surface (forearm and fingertip) were significantly lower than tympanic membrane temperatures. Differences between temperatures of the tympanic membrane and those at peripheral sites decreased during the first 40 min of surgery, but remained 1–2°C throughout the study.

The differences between tympanic membrane and esophageal temperatures during the first 60 min of surgery in the three study groups appear in Figure 2. Although esophageal and tympanic membrane temperatures in the entire group were similar, esophageal temperatures in patients receiving active and passive airway humidification were about 0.35°C above tympanic temperatures after induction of anesthesia. In contrast, esophageal temperatures in patients without airway humidification were 0.25°C below tympanic temperatures after induction of an-

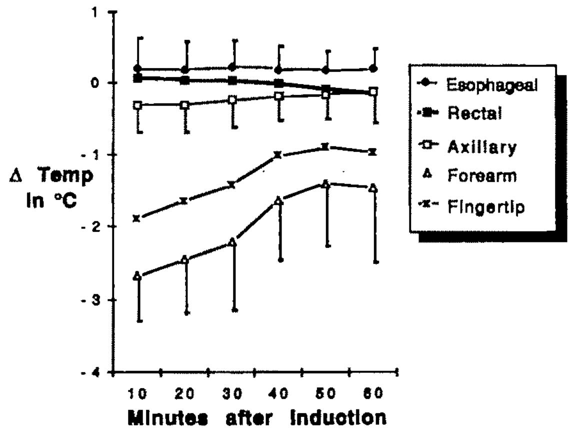


Figure 1. The average difference between temperatures at five different measurement sites and tympanic membrane temperature in 20 children weighing 5–30 kg. The central sites (esophagus, rectum, and axilla) did not differ significantly, whereas the temperatures of the peripheral skin surface (forearm and fingertip) were significantly lower than the central temperatures. Vertical bars illustrate the standard deviation. Standard deviations of the rectal temperatures (omitted for clarity) were similar to those of the esophageal and axillary temperatures. Standard deviations of fingertip temperatures were similar to those of the forearm temperatures.

esthesia. Esophageal–tympanic membrane temperature differences in the patients given active and passive humidification differed significantly from the corresponding sum in the control group at all times, but not from each other. The deviations from tympanic temperature decreased during the study period.

Discussion

Temperature monitoring sites have been considered valid when they compared favorably with tympanic (e.g., hypothalamic) temperature (1). There is little physiological support for an exclusive reliance on tympanic membrane temperature since it is now known that integrated input from the entire body determines thermoregulatory responses. Evidence in mammals and birds indicates that multiple, redundant thermal inputs from nearly every part of the body are integrated by both the spinal cord and hypothalamus (4–13). It is likely that thermal sensing is similar in humans. Thus, the most useful approach to temperature monitoring is to recognize that temperatures of different tissues are "real," but that the physiological and practical significance of each varies.

In unanesthetized humans, tympanic, rectal, and esophageal temperatures are usually similar, so that any one reflects most of the noncutaneous input to the thermoregulatory system. Temperatures at these sites also are similar in anesthetized adults undergoing noncardiac surgery (1). The statistically nonsignificant temperature differences we observed between these measurement sites (approximately 0.2°C) in our patients were small compared to the range of "normal" temperatures in humans (approximately 1°C); the differences were extremely small compared with the temperature decrease required to trigger intraoperative thermoregulatory responses (approximately 2.5°C) (14,15). Thus, tympanic, esophageal, or rectal temperatures also reflect the bulk of central thermoregulatory input in anesthetized children undergoing noncardiac surgery.

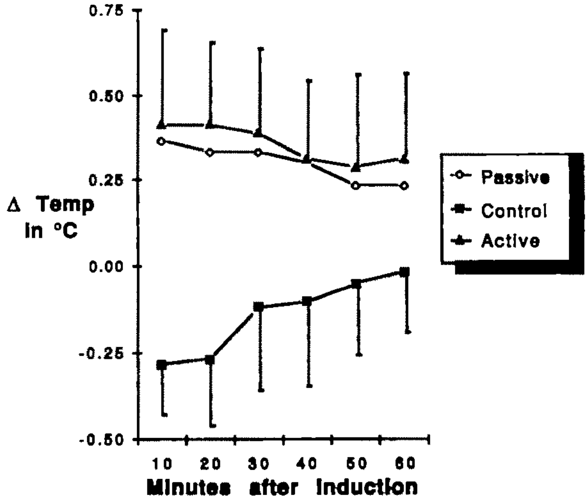


Figure 2. The mean difference between esophageal temperature and tympanic membrane temperature during the first 60 min of surgery in children receiving different airway humidification and/or heating. The control group (N = 6) received no airway humidification of heating. The passive group (N = 6) had a Humid-Vent 1 heat and moisture exchanger placed between the endotracheal tube connector and the Ayre's *t*-piece. The active group (N = 8) was given respiratory gases humidified to nearly 100% and heated to approximately 37°C by a Fisher and Paykel heater/humidifier. Although esophageal and tympanic membrane temperatures in the entire group were similar (Figure 1), esophageal temperatures in patients receiving active and passive airway humidification were about 0.35°C above tympanic temperatures after induction of anesthesia. In contrast, esophageal temperatures in patients without airway humidification were 0.25°C below tympanic temperatures after induction of anesthesia. Esophageal–tympanic membrane temperature differences in the patients given active and passive humidification differed significantly from temperatures in the control group at all times, but not from each other.

Axillary temperatures were not significantly different from other central temperatures in the infants and children in this study, although they correlated poorly in a previous study in adults (1). A potentially important difference is that we carefully positioned the thermocouple over the axillary artery in this study, but no special positioning was used in the adult study. It is likely that thermocouple position is more important than patient size.

Determinations of skin temperature are useful because 10–20% of the input to thermoregulatory system is derived from the skin surface (6). Thermoregulatory vasoconstriction also can be easily detected by measuring skin surface gradients (fingertip temperature–forearm temperature) (14,15). In adults, peripheral skin surface temperatures correlate poorly with central temperatures (1); we observed a similarly poor correlation in these infants and children. Not only were temperatures of the skin surface significantly lower than central temperatures, but the difference between skin and central temperatures decreased by approximately 1°C during anesthesia. Thus, simply adding a constant value (e.g., 3°C) to an arbitrary skin temperature, such as the forehead, is unlikely to provide adequate indication of central temperature.

As reported by others in adults (1), we found that fingertip temperatures were higher than forearm temperatures. However, thermoregulatory vasoconstriction can decrease fingertip temperature by 10°C (14,15). Had these children been sufficiently hypothermic to trigger thermoregulatory vasoconstriction, the differences between fingertip and tympanic temperatures might have been much greater. Hypotension or light levels of anesthesia may also increase this temperature difference.

Temperature measured in the upper esophagus can be approximately 1°C lower than that in the retrocardiac portion in anesthetized, intubated patients (2). Presumably, the upper esophagus is cooler because some metabolic heat is eliminated by adjacent respiratory gas flow. However, respiratory gases are thought to influence temperature in the retrocardiac portion of the esophagus minimally. We found that lower esophageal temperatures were approximately 0.35°C above tympanic membrane temperatures in patients given passively or actively humidified respiratory gases. In contrast, lower esophageal temperatures were approximately 0.25°C below tympanic membrane temperatures in the control patients given unconditioned gases via an open, high flow anesthesia system. Although these differences are relatively small, they suggest that the benefits of airway warming and/or humidification may be overestimated when central temperature is measured in the lower esophagus.

The results of this study may not apply to patients given other anesthetics, to other anesthesia delivery systems, to infants weighing <5 kg, or to children weighing >30 kg. It is likely that temperature differences between the central measurement sites would have been larger had our population included patients undergoing neurological and major abdominal operations. Although we did not calibrate the sterile, disposable thermocouples used in this study, extensive testing by Mon-a-Therm and the investigators confirms that the accuracy of these probes is within 0.1°C.

Recorded temperatures may deviate from the "true" temperature because 1) the thermometer is imprecise (i.e., recorded thermometer temperature may differ from that of the probe), 2) the temperature of the probe differs from that of the surrounding tissue (i.e., an artifactual reading), or 3) temperature of the probe (in a convenient location) differs from the temperature of interest (in a poorly accessible tissue such as the brain). Most clinical thermistors and thermocouples have an accuracy of approximately 0.1°C (R. Reeves, personal communication). This value is small compared to physiological population variation (approximately 1°C) so thermometer failure per se is rarely clinically important.

Artifactual reading results when thermometer temperature is altered by factors that do not influence temperature of the surrounding tissue. This error could result, for example, when a rectal probe is imbedded in a fecal mass: indicated temperature may be increased by bacterial metabolic heat, or insulating properties of the mass may delay detection of rapid temperature changes in the surrounding tissues. Ambient air temperature also may artifactually lower indicated temperatures when aural probes are not carefully placed in contact with the tympanic membrane. For similar reasons, thermometers combined with endotracheal tubes have not generally proved useful.

In summary, esophageal, rectal, and axillary temperatures in infants and children given halothane/nitrous oxide anesthesia for noncardiac surgery rarely differed from tympanic membrane temperatures by more than 0.2°C. This difference was not statistically significant, was small compared with the physiological differences between individuals, and indicates that any one reflects the bulk of central thermoregulatory input. In contrast, temperatures at the forearm and fingertip skin surface were significantly different from tympanic membrane temperature, indicating that skin surface measurements are not a substitute for determining central temperatures. Esophageal temperatures were slightly, but significantly, increased when patients were ventilated with warmed and/or humidified respiratory gases.

The authors greatly appreciate helpful discussions with Randi Støen, M.D. and acknowledge the editorial advice of Winifred von Ehrenburg. The thermometers and thermocouples we used were generously donated by Mon-a-Therm Inc., Richard Reeves, Technical Director.

References

1. Cork RC, Vaughan RW, Humphrey LS. Precision and accuracy of intraoperative temperature monitoring. Anesth Analg 1983; 62:211–4.
2. Kaufman RD. Relationship between esophageal temperature gradient and heart and lung sounds heard by esophageal stethoscope. Anesth Analg 1987;66:1046–8.
3. Rose DK, Froese AB. The regulation of Pa_{CO_2} during controlled ventilation of children with a *t*-piece. Can Anaesth Soc J 1979;26:104–13.
4. Simon E, Pierau FK, Taylor DCM. Central and peripheral thermal control of effectors in homeothermic temperature regulation. Physiol Rev 1986;66:235–300.
5. Simon E. Temperature regulation: the spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev Physiol Biochem Pharmacol 1974;71:1–76.
6. Benzinger TH, Pratt AW, Kitzinger C. The thermostatic control of human metabolic heat production. Proc Natl Acad Sci USA 1961;47:730–9.
7. Rawson RO, Quick KP. Evidence of deep-body thermoreceptor response to intra-abdominal heating of the ewe. J Appl Physiol 1970;28:813–20.
8. Mercer JB, Jessen C. Central thermosensitivity in conscious goats: hypothalamus and spinal cord versus residual inner body. Pflügers Arch 1978;374:179–86.
9. Riedel W, Siaplauras G, Simon E. Intra-abdominal thermosensitivity in the rabbit as compared with spinal thermosensitivity. Pflügers Arch 1973;340:59–70.
10. Jessen C, Feistkorn G. Some characteristics of core temperature signals in the conscious goat. Am J Physiol 1984;247:R456–64.
11. Colin J, Timbal J, Houdas Y, Boutelier C, Guieu JD. Computation of mean body temperature from rectal and skin temperatures. J Appl Physiol 1971;31:484–9.
12. Stolwijk JAJ, Hardy JD. Partitional calorimetric studies of responses of man to thermal transients. J Appl Physiol 1966; 21:967–77.
13. Ramanathan NL. A new weighting system for mean surface temperature of the human body. J Appl Physiol 1964;19:531–3.
14. Sessler DI, Olofsson CI, Rubinstein EH, Beebe J. The thermoregulatory threshold during halothane anesthesia in humans. Anesthesiology 1988;68:836–42.
15. Sessler DI, Olofsson CI, Rubinstein EH. The thermoregulatory threshold in humans during nitrous oxide/fentanyl anesthesia. Anesthesiology 1988;69:357–64.

ANESTH ANALG 1989;69:197–201

Pituitary-Adrenal Stress Response in the Absence of Brain-Pituitary Connections

Daniel B. Carr, MD, Jane C. Ballantyne, MB BS, Patricia F. Osgood, PhD,
James W. Kemp, BS, and Stanislaw K. Szyfelbein, MD

CARR DB, BALLANTYNE JC, OSGOOD PF, KEMP JW, and SZYFELBEIN SK. Pituitary-adrenal stress response in the absence of brain-pituitary connections. Anesth Analg 1989;69:197–201.

To examine whether an acute pituitary-adrenal response to stress may occur in vivo in the absence of hypothalamic–pituitary connections, we measured plasma β-endorphin (β-EP) and corticosterone (C) in rats after acute thermal injury. β-EP rose significantly after thermal injury in normal rats and rats bearing pituitary-to-kidney autotransplants but not in animals with pituitary aspiration without reimplantation. Corticosterone responses paralleled β-EP but were significant only in normal controls. Propranolol pretreatment did not reduce postburn β-EP and C rises in autotransplanted animals. Therefore, since circulating factors contribute in vivo to pituitary-adrenal responses, the widespread practice of using "stress hormone" responses to quantitate perioperative stress or pain may in some circumstances be flawed.

Key Words: HORMONES—corticosterone. BRAIN, PITUITARY-ADRENAL AND HYPOTHALAMIC—pituitary connections. BRAIN—endorphins.

Classical neuroendocrine physiology depicts the activation of the pituitary-adrenal axis as under exclusive control of the central nervous system (CNS). In this view, peripheral tissue injury leads to nociceptive afferent input to the CNS, which culminates in hypothalamic releasing-hormone secretion and subsequent pituitary and adrenal hormone release (1). Based upon this view, innumerable studies of analgesics' effects on perioperative stress or pain have relied upon blood hormone measurements to quantitate CNS responses during surgery and anesthesia. Yet extra-CNS factors capable of contributing to the pituitary–adrenal stress hormone response have long been suggested (2–4). Recent studies have found direct actions of monokines such as interleukin-1 upon pituitary cells in vitro (5,6) or indirect actions such as depletion of hypothalamic corticotropin-releasing hormone (CRH) (7,8). Nonetheless, the question of whether extra-CNS factors contribute in vivo to acute pituitary–adrenal stress responses has remained controversial (9). In particular, this question has not been addressed in relation to burn injury although this is recognized to result in pronounced hypercortisolemia, metabolic and immune derangements, and difficult problems in pain management necessitating use of potent analgesics (10–15).

To distinguish peripheral (i.e., blood-borne via the systemic circulation) from central (i.e., hypothalamic-hypophyseal humoral or neural) signals mediating the pituitary–adrenal stress response, we employed animals with autotransplantation of the pituitary from sella turcica to under the renal capsule. Heterotopic pituitary autotransplantation is a venerable technique for preserving pituitary tissue while disrupting any possible brain-pituitary connection (16–18). It averts the potentially confounding effects of persistent high local concentrations of hypothalamic releasing factors near a pituitary left *in situ* after stalk section, or regrowth of neural connections down the pituitary stalk.

Methods

All experiments were reviewed and approved by the Protocol Review Group of the Subcommittee on Animal Care, Committee on Research, Massachusetts General Hospital. Male Sprague-Dawley rats (Taconic

---

This work was supported by the Shriners Burns Institute grants 15898 and 15899.

Received from the Analgesic Peptide Research Unit and Departments of Anesthesia and Medicine, Shriners Burns Institute, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts. Accepted for publication March 13, 1989.

Address correspondence to Dr. Carr, Shriners Burns Institute, 51 Blossom Street, Boston MA 02114.

©1989 by the International Anesthesia Research Society

Farms, Inc., Germantown, NY) weighed 175–200 g. Under sodium pentobarbital anesthesia, pituitaries were gently aspirated via the auditory canal using a needle and glass syringe in 34 rats. Each aspirate was discharged into a petri dish and inspected to assure completeness of removal. In 24 of these animals, the pituitary was placed in a petri dish filled with phosphate-buffered saline (pH 7.4). These animals then had the abdominal wall opened via a separate, 2-cm dorsal midline incision, through which a kidney was retracted. The pituitary gland was then placed in a trochar and implanted under the kidney capsule, after which the kidney was returned to the body cavity and the skin incision closed. Ten animals did not undergo pituitary reimplantation, i.e., were left with hypophysectomies. Autotransplanted or hypophysectomized animals were kept on 12-h light–dark cycles and given free access to lab chow and 5% dextrose in water. Chronic indwelling jugular cannulae were placed in these and 12 intact normal rats after preoperative penicillin (50,000 U intramuscular), atropine (0.01 mg subcutaneous), and, in hypophysectomized or autotransplanted rats, hydrocortisone (5 mg/kg intraperitoneal). Ketamine anesthesia (50 mg/kg intraperitoneal) was used for cannula implantation in all groups as this technique produced less cardiovascular instability than other anesthetic regimens tested (e.g., barbiturates).

Plasma immunoreactive β-endorphin (B-EP) (19) and corticosterone (C) (Cambridge Medical Diagnostics, Billerica MA) were assayed by published methods. Cutoff levels of 2000 pg/ml and 500 μg/ml were used for B-EP and C, respectively, because higher values were imprecise in the assay conditions employed.

Atraumatic sampling of plasma for hormone assays was carried out before and 30 min after injection of saline vehicle on a control day, day 0. Starting the next morning, day 1, in order to detect incomplete hypophysectomies (20,21) or unsuccessful autotransplants, animals in these two experimental groups were primed twice daily for three days with 1 μg of subcutaneous ovine CRH (22; Bachem, Torrance, CA). On days 1–3, plasma was sampled immediately before and 30 min after the morning CRH injection and assayed for B-EP and C (Table 1). B-EP and C showed no response to CRH in 4 out of 24 autotransplanted animals and their results were excluded from any analyses. On day 4, animals were subjected to a thermal stress previously found to raise B-EP levels in normal, intact rats (23): rats were pretreated with atropine (0.01 mg subcutaneous) and anesthetized with pentobarbital (25 mg/kg intraperitoneal) prior to scald of 50% body surface area. Half of the remaining autotransplanted group ($n = 10$) received propranolol (500 μg intraperitoneal) 45 min prior to burn. Twelve intact normal rats underwent acute burn only without CRH priming.

A two-tailed paired t-test was applied within the autotransplanted group to determine the significance of differences between mean hormone levels before and after acute CRH administration on each day (24). To assess the effect of acute burn stress upon plasma levels of B-EP and C during the next three hours, we did not employ multiple t-tests at consecutive time points because doing so might have produced spuriously low P values (25,26). Instead, we calculated an integrated response, the area under the time-course curve above the basal level, as a summary measure of the time course of each of these two hormones. This integrated response was computed using the trapezoidal rule program developed by Tallarida and Murray (24). A single t-test was then used to examine whether the integrated response was greater than zero in each experimental group.

Results

Normal, intact animals showed robust rises in both B-EP and C (Table 1), confirming previous findings (23). Animals with pituitary excision (without reimplantation) had minor, insignificant rises in B-EP and C.

In rats with pituitary-to-kidney autotransplants, injections of CRH on days 1, 2, and 3 produced concurrent, significant rises in both B-EP and C (Table 1). In contrast, insignificant increases in B-EP (67 ± 32 to 126 ± 90 pg/ml; mean ± SEM) and insignificant decreases in C (19 ± 23 to 11 ± 2 ng/ml) were seen after saline vehicle injection on day 0. Autotransplanted rats had increases in B-EP after burn injury, although their absolute B-EP levels were between those of the hypophysectomized and intact groups. Propranolol pretreatment in the autotransplanted group was associated with a slightly greater B-EP peak response, than without pretreatment. Statistically insignificant increases in C to a peak of about twice the baseline were present in both autotransplanted groups, although numerically higher levels of C at all time points were found after propranolol pretreatment.

Positive but insignificant correlations (range 0.37–0.47) were present between B-EP and C in each of the three operated groups after acute burn, but only for the unoperated, intact controls was r significant [0.96, $P < 0.0001$].

Table 1. Mean Levels of Plasma Immunoreactive β-Endorphin and Corticosterone

Group/Day/Treatment	β-Endorphin (pg/ml)	Corticosterone (μg/ml)
Normal, intact (N = 12)		
Burn, T = 0 (min)	314 (77)	159 (76)
30	1115 (159)	500 (0)
60	1151 (155)	491 (9)
90	1201 (173)	500 (0)
120	981 (100)	500 (0)
180	836 (192)	500 (0)
	($t = 5.49$, $P < 0.001$)	($t = 4.36$, $P < 0.02$)
Hypophysectomized (N = 10)		
Day 1, pre-CRH	16 (4)	16 (0.3)
post-CRH	11 (2)	16 (0.9)
Day 2, pre-CRH	17 (3)	15 (1)
post-CRH	8 (2)	15 (0.6)
Day 3, pre-CRH	15 (2)	16 (0.6)
post-CRH	14 (4)	15 (0.4)
Day 4, burn T = 0 (min)	42 (5)	20 (2)
30	50 (5)	23 (1)
60	66 (10)	24 (3)
90	52 (6)	22 (2)
120	39 (7)	19 (2)
180	44 (13)	19 (2)
	(NS)	(NS)
Autotransplant (N = 10)		
Day 1, pre-CRH	59 (9)	7 (0.4)
post-CRH	343 (38)^{c}	14 (1)^{c}
Day 2, pre-CRH	61 (12)	8 (0.5)
post-CRH	295 (21)^{d}	24 (3)^{c}
Day 3, pre-CRH	67 (9)	9 (1)
post-CRH	392 (34)^{c}	31 (5)^{a}
Day 4, burn, T = 0 (min)	67 (10)	8 (0.6)
30	182 (27)	24 (10)
60	146 (24)	20 (8)
90	131 (28)	16 (6)
120	142 (31)	12 (3)
180	178 (34)	10 (3)
	($t = 4.28$, $P < 0.01$)	(NS)
Beta-blocked autotransplant (N = 10)		
Burn, T = 0 (min)	65 (11)	36 (5)
30	171 (24)	55 (12)
60	352 (95)	65 (18)
90	277 (67)	45 (5)
120	294 (76)	48 (5)
180	444 (53)	57 (9)
	($t = 2.84$, $P < 0.02$)	(NS)

Values given as means (SEM). *P*-values for the responses to acute CRH are denoted by ^{a} <0.05, ^{b} <0.01, ^{c} <0.001, ^{d} <0.0001. See Methods for description of statistical tests employed in each experimental condition. Abbreviations: CRH, corticotropin-releasing hormone; NS, nonsignificance.

Discussion

These results demonstrate in vivo an acute pituitary–adrenal response to tissue damage in the absence of direct control by the CNS. That is, after acute burns peripheral, systemically circulating factors appear to mediate a B-EP response only moderately less than that evoked by a pharmacologic dose of hypothalamic CRH. The near-absence of B-EP or C increases in hypophysectomized rats after CRH or burn injury indicates that postburn B-EP increases in autotransplanted rats result essentially from the heterotopic pituitaries only, and not other tissues, pituitary remnants, or white blood cells (27–29). Of course, the present results do not define the structure or source of circulating CRH-like bioactivity, a complex task given the known presence of hypothalamic and nonhypothalamic contributions to circulating "authentic" CRH (30–32), the extra-hypothalamic origin of "tissue" CRH (16–18), and the presence of IL-1 in hypothalamic tissues (33).

Our data thus extend older investigations (i.e., before the advent of radioimmunoassays) which suggested that peripheral factors of extrahypothalamic origin may reach the pituitary via the systemic circulation and thereby directly stimulate pituitary-adrenal stress responses (16–18). Recent interest in such factors has intensified after the demonstration that monokines may stimulate pituitary cells in vitro to secrete adrenocorticotropic hormone (ACTH), yet ongoing studies of this complex process (34) have produced conflicting results (9). Bernton and co-workers (6), for example, found that IL-1 directly releases ACTH and other hormones from cultured pituicytes, while others (7,8,35,36) have suggested that interleukin-1 acts in vitro or in vivo to stimulate CRH secretion and only secondarily evokes pituitary ACTH secretion. Moreover, our data further extend observations that in vivo immune neutralization of CRH (37,38) or isolation of the pituitary from its hypothalamic control (39) may be insufficient to suppress entirely the pituitary-adrenal response to acute stress, and that plasma B-EP levels are many-fold higher during hypotension due to endotoxin compared with that due to hemorrhage (40).

Although the pituitary-to-kidney autotransplant model is still in use, it has been applied largely to study chronic hyperprolactinemia (41) rather than acute pituitary-adrenal responses. Neurointermediate (not anterior) lobe autotransplants to kidney have recently been reported, however (42). We chose not to employ multiple pituitary grafts per animal to avoid possible high baseline corticosterone levels in such animals (16–18,41).

The importance of β-adrenergic pathways in pituitary–adrenal responses to certain stressors (e.g., hypoglycemia) is recognized (43), but in our hands propranolol augmented stress-induced B-EP and C secretion. We cannot exclude the possibility that circulating catecholamines may affect the secretory activity of heterotopic pituitary tissue. Nonetheless, this appears unlikely in view of results by Makara et al. (44) that β-adrenergic blockade has little effect on stress-induced pituitary ACTH secretion in rats with hypothalamic deafferentation. It is unclear why plasma B-EP and C levels were higher at nearly all time points in the β-blocked group than in the untreated autotransplanted animals, although replication and clarification of this effect might shed light on regulation of stress-induced pituitary–adrenal secretion.

Our findings indicate that stress hormone release may to some degree be independent of, and hence may not always parallel, CNS processes. Thus, the widespread practice of quantitating stress or pain perceived by the CNS through measurements of circulating "stress hormones" (1,4,22,45), even to the point of titrating perioperative analgesic drug doses to suppress these hormonal responses (46), may be flawed. Further studies will be necessary to assess the relative importance in vivo of many mediators (e.g., interleukins or other factors (47) with CRH-like activity) that might contribute to our present findings. For such studies, the pituitary-to-kidney autotransplanted rat model is attractive.

We thank J. Barvik and A. Kazianis for outstanding technical support, Dr. H. Bode for useful discussions, and P. Meara for pilot corticosterone assays.

References

1. Axelrod J, Reisine TD. Stress hormones: their interaction and regulation. Science 1984;226:452–9.
2. Gordon ML. An evaluation of afferent nervous impulses in the adrenal cortical response to trauma. Endocrinology 1950; 47:347–50.
3. Lymangrover J, Brodish A. Tissue CRF: an extrahypothalamic corticotrophin releasing factor (CRF) in the peripheral blood of stressed rats. Neuroendocrinology 1973;12:225–35.
4. Yasuda N, Greer MA, Aizawa T. Corticotropin-releasing factor. Endocr Rev 1982;3:123–40.
5. Woloski BMRNJ, Smith EM, Meyer WJ, Fuller GM, Blalock JE. Corticotropin-releasing activity of monokines. Science 1985; 230:1035–7.
6. Bernton EW, Beach EJ, Holaday JW, Smallridge RC, Fein HG. Release of multiple hormones by a direct action of interleukin-1 on pituitary cells. Science 1987;238:519–21.
7. Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science 1987;238:522–4.
8. Berkenbosch F, van Oers J, del Rey A, Tilders F, Besedovsky H. Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. Science 1987;238:524–7.
9. Lumpkin MD: The regulation of ACTH secretion by interleukin-1. Science 1987;238:452–4.
10. Butterfield WJH. The endocrine response to burning injury. Proc R Soc Med 1954;47:228–9.
11. Hume DM, Nelson DH, Miller DV. Blood and urinary 17-hydroxycorticosteroids in patients with severe burns. Ann Surg 1956;143:316–29.
12. Batstone GF, Hinks L, Whitefoot R, Bloom S, Laing JE, Alberti KGMM. Hormonal changes after thermal injury. Burns 1976; 2:207–25.
13. Miller SE, Miller CL, Trunkey DD. The immune consequences of trauma. Surg Clin N Am 1982;62:167–83.
14. Davis JWL. Physiological responses to burning injury. New York: Academic Press, 1982.
15. Antonacci AC, et al. Autologous and allogeneic mixed-lymphocyte responses following thermal injury in man: the immunomodulatory effects of interleukin 1, interleukin 2, and a prostaglandin inhibitor, WY-18251. Clin Immunol Immunopathol 1984;38:304–20.
16. Cheng C, Sayers G, Goodman LS, Swinyard CA. Discharge of adrenocorticotrophic hormone from transplanted pituitary tissue. Am J Physiol 1949;159:426–32.

17. Fortier C, Selye H. Adrenocorticotrophic effect of stress after severance of the hypothalamo-hypophyseal pathways. Am J Physiol 1949;159:433–9.
18. Nikitovitch-Winer M, Everett JW. Functional restitution of pituitary grafts re-transplanted from kidney to median eminence. Endocrinology 1958;63:916–30.
19. Carr DB, et al. Endotoxin-stimulated opioid peptide secretion: two pools and feedback control in vivo. Science 1982; 217:845–8.
20. Dunn AJ, Powell ML, Gaskin JM. Virus-induced increases in plasma corticosterone. Science 1987;238:1423–4.
21. Blalock JE. Virus-induced increases in plasma corticosterone. Science 1987;238:1424–5.
22. Rivier C, Brownstein M, Spiess J, Rivier J, Vale W. In vivo corticotropin-releasing factor-induced secretion of adrenocorticotropin, beta-endorphin and corticosterone. Endocrinology 1982;110:272–8.
23. Osgood PF, Murphy JL, Carr DB, Szyfelbein SK. Increases in plasma beta-endorphin and tail flick latency in the rat following burn injury. Life Sci 1987;40:547–54.
24. Tallarida RJ, Murray RB. Manual of pharmacologic calculations with computer programs. 2nd ed. New York: Springer-Verlag, 1987:77–9.
25. Petrinovich LF, Hardyck CD. Error rates for multiple comparison methods: some evidence concerning the frequency of erroneous conclusions. Psychol Bull 1969;71:43–54.
26. Elashoff JD. Down with multiple t-tests! Gastroenterology 1981;80:615–20.
27. Lolait SJJ, et al. Proopiomelanocortin messenger ribonucleic acid and posttranslational processing of endorphin in spleen macrophages. J Clin Invest 1986;77:1776–9.
28. Smith EM, Meyer WJ, Blalock JE. Virus-induced corticosterone in hypophysectomized mice: a possible lymphoid adrenal axis. Science 1982;218:1311–2.
29. Smith EM, Blalock JE. Human lymphocyte production of corticotropin and endorphin-like substances: association with leukocyte interferon. Proc Natl Acad Sci USA 1981;78:7530–4.
30. Kruseman ACE, Linton EA, Ackland J, Besser GM, Lowry PJ. Heterogeneous immunocytochemical reactivities of oCRF-41-like material in the human hypothalamus, pituitary and gastrointestinal tract. Neuroendocrinology 1984;38:212–6.
31. Suda T, Tomori N, Tozawa F, Mouri T, Demura H, Shizume K. Distribution and characterization of immunoreactive corticotropin-releasing factor in human tissues. J Clin Endocrinol Metab 1984;59:861–6.
32. Sasaki A, et al. Immunoreactive corticotropin-releasing hormone present in human plasma may be derived from both hypothalamic and extrahypothalamic sources. J Clin Endocrinol Metab 1987;65:176–82.
33. Breder CD, Dinarello CA, Saper CB. Interleukin-1 immunoreactive innervation of the human hypothalamus. Science 1988; 240:321–4.
34. Besedovsky H, del Rey A, Sorkin E, Dinarello CA. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. Science 1986;233:652–4.
35. Uehara A, Gillis S, Arimura A. Effects of interleukin-1 on hormone release from normal rat pituitary cells in primary culture. Neuroendocrinology 1987;45:343–7.
36. Uehara A, Gottschall PE, Dahl RR, Arimura A. Interleukin-1 stimulates ACTH release by an indirect action which requires endogenous corticotropin releasing factor. Endocrinology 1987;121:1580–3.
37. Linton EA, et al. Stress-induced secretion of adrenocorticotropin in rats is inhibited by administration of antisera to ovine corticotropin-releasing factor. Endocrinology 1985;116:966–70.
38. Giuffre KA, Udelsman, Listwak S, Chrousos GP. Effects of immune neutralization of corticotropin-releasing hormone, adrenocorticotropin, and beta-endorphin in the surgically stressed rat. Endocrinology 1988;122:306–10.
39. Egdahl RH. Corticosteroid secretion following caval constriction in dogs with isolated pituitaries. Endocrinology 1961; 68:226–31.
40. Hamilton AJ, Carr DB, LaRovere J, Black PMcL. Endotoxic shock elicits greater endorphin secretion than hemorrhage. Circ Shock 1986;19:47–54.
41. Adler R. The anterior pituitary-grafted rat: a valid model of chronic hyperprolactinemia. Endocr Rev 1986;7:302–13.
42. Antakly T, Sasaki A, Liotta AS, Palkovits M, Krieger DT. Induced expression of the glucocorticoid receptor in the rat intermediate pituitary lobe. Science 1985;229:277–9.
43. Mezey E, Reisine TD, Brownstein MJ, Palkovits M, Axelrod J. Beta-adrenergic mechanism of insulin-induced adrenocorticotropin release from the anterior pituitary. Science 1984; 226:1085–7.
44. Makara GB, Kvetnansky R, Jezova D, Jindra A, Kakucska I, Oprasalova Z. Plasma catecholamines do not participate in pituitary-adrenal activation by immobilization stress in rats with transection of nerve fibers to the median eminence. Endocrinology 1986;119:1757–62.
45. Szyfelbein SK, Osgood PF, Carr DB. The assessment of pain and plasma beta-endorphin immunoactivity in burned children. Pain 1985;22:173–82.
46. Estafanous FG, ed. Opioids in anesthesia. Boston: Butterworths, 1984.
47. Margreaves KM, Costello AH, Joris JL. Release from inflamed tissue of a substance with properties similar to corticotropin-releasing factor. Neuroendocrinology 1989;49:476–82.

ANESTH ANALG
1989;69:202–6

Esmolol for Potentiation of Nitroprusside-Induced Hypotension:

Impact on the Cardiovascular, Adrenergic, and Renin-Angiotensin Systems in Man

Richard Edmondson, MD, Oscar Del Valle, MD, Nitin Shah, MD, George Wong, PhD, Donna Dwyer, CRNA, Deborah Matarazzo, CRNA, Alisa Thorne, MD, Charles Coffey, MD, and Robert Bedford, MD

EDMONDSON R, DEL VALLE O, SHAH N, WONG G, DWYER D, MATARAZZO D, THORNE A, COFFEY C, BEDFORD R. Esmolol for potentiation of nitroprusside-induced hypotension: impact on the cardiovascular, adrenergic, and renin-angiotensin systems in man. Anesth Analg 1989;69:202–6.

Esmolol infusion at rates of 200, 300, and 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *was used to potentiate hypotension (mean arterial pressure = 60 mm Hg) induced with sodium nitroprusside (SNP) in 10 male patients undergoing radical cancer surgery during nitrous oxide-oxygen and fentanyl anesthesia. Heart rate (HR), blood pressure (radial arterial catheter), and plasma levels of renin activity (PRA), norepinephrine (N), epinephrine (E), and dopamine (D) were measured: 1) while patients were awake; 2) after induction of anesthesia (nitrous oxide, 60% in oxygen, fentanyl = 5* $\mu g/kg$ *followed by an infusion at 10* $\mu g \cdot kg^{-1} \cdot hr^{-1}$*); 3) after surgery had begun; 4) after 20 minutes of SNP-induced hypotension; 5) after 20 minutes of esmolol at each of the above infusion rates; and 6) after the completion of surgery. Compared to awake values, SNP-induced hypotension (mean infusion rate = 3.1* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *± 0.6* SE*) during surgery resulted in significant (*$P < 0.05$*) increases in heart rate, PRA, N, and D. Infusion of esmolol resulted in significant (*$P < 0.05$*) dose-dependent reductions in SNP requirement to maintain MAP = 60 mm Hg. At 200* $\mu g \cdot kg^{-1} \cdot min^{-1}$*, SNP requirement was 2.1* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *±0.4, at 300* $\mu g \cdot kg^{-1} \cdot min^{-1}$*, it was 1.0* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *±0.2, and at 400* $\mu g \cdot kg^{-1} \cdot min^{-1}$*, was 0.5* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *±0.3. Concomitant with the decrease in SNP requirement, there were significant reductions in HR and PRA at all infusion rates of esmolol. At 300* $\mu g \cdot kg^{-1} \cdot min^{-1}$*, there was a significant (*$P < 0.05$*) increase in* PaO_2 *(141 mm Hg ± 18 to 162 mm Hg ± 16, and decrease in N (615 pg/ml ± 105 to 356 pg/ml ± 56) and E (74 pg/ml ± 20 to 57 ± 10). No rebound hypertension was observed at the end of SNP-esmolol infusion, and HR, BP,* PaO_2*, PRA, N, and D levels were not different from awake values. Only E levels were elevated postoperatively (460 pg/ml ± 98 vs 63 pg/ml ± 8 preoperatively,* $P < 0.05$*). The authors conclude that esmolol infusion is a safe and effective pharmacologic means of potentiating SNP-induced hypotension during fentanyl-*N_2O*-*O_2 *anesthesia. Esmolol acts by counteracting many of the adverse endocrine and baroreceptor-mediated effects of SNP, and the short half-lives of esmolol and SNP permit contemporaneous termination of action when they are simultaneously discontinued.*

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE—nitroprusside. HEART, MYOCARDIAL FUNCTION. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol.

Sodium nitroprusside (SNP) is widely used for inducing intraoperative hypotension despite its well-known disadvantages, including tachyphylaxis (1,2), reflex tachycardia (1–4), the possibility of cyanide toxicity (5–11), deterioration in arterial oxygenation (12,13), and rebound hypertension (14). Some of the techniques for reducing dose requirements for SNP and its attendant complications include increasing doses of general anesthetics (15,16), use of converting enzyme inhibitors (17,18), and beta adrenergic blockade (19–21). Propranolol has been the most widely recommended beta-blocking agent for use in conjunction with SNP, but it has a relatively slow onset, a

---

Received from Departments of Anesthesiology and Critical Care Medicine and Biostatistics and Epidemiology, Memorial Sloan-Kettering Cancer Center, and Cornell University Medical College, New York, NY. Accepted for publication December 12, 1988.

Address correspondence to Dr. Bedford, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

©1989 by the International Anesthesia Research Society

duration of action that may prevent tachycardia indicative of postoperative hypoxemia or hypovolemia, and a lack of beta-1 antagonism that may be troublesome in patients with reactive airways disease. The recently introduced short-acting beta blocker, esmolol, has the advantages of beta-1 antagonism, rapid onset and brief half-life, thus theoretically making it an ideal agent for potentiation of SNP-induced hypotension (22–24). We sought to evaluate these potential advantages by studying the impact of esmolol infusion on SNP dose-requirement, arterial oxygenation, heart rate, plasma renin activity, and catecholamine levels during SNP-induced hypotension to a mean arterial blood pressure of 60 mm Hg in patients undergoing major cancer operations.

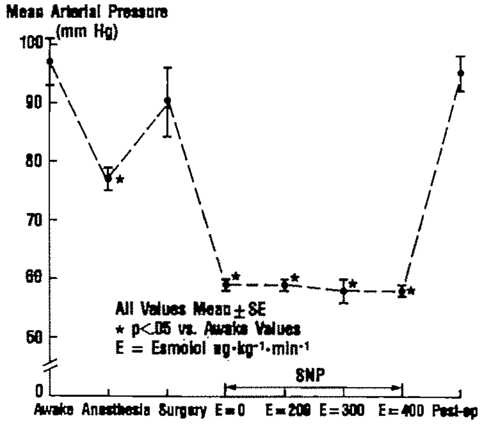


Figure 1. Mean arterial blood pressure during the study. Note the absence of rebound hypertension in the postoperative period.

Methods

The subjects of this investigation were 10 ASA physical status I or II patients, ages 25–75 years (mean = 47) with urological malignancies scheduled for radical abdominal operations. The protocol was reviewed and approved by the Institutional Review Board, and informed consent was obtained from each patient on the day before operation. Premedication consisted of meperidine, 1 mg/kg, hydroxyzine, 1 mg/kg, and glycopyrolate, 0.2 mg, IM one hour before the operation. Anesthesia was induced with thiopental, 3–5 mg/kg, and maintained with 60% N_2O in oxygen supplemented with fentanyl, 5 μg/kg IV, followed by a fentanyl infusion at a rate of 5–10 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ throughout the operation. Tracheal intubation was facilitated with succinylcholine, 1 mg/kg, IV, and abdominal muscle relaxation was maintained with pancuronium, 0.1 mg/kg IV, as required. Ventilation was controlled to maintain end-tidal CO_2 tension at 35 mm Hg (Perkin-Elmer Mass Spectrograph) and central venous and radial arterial catheters were placed for continuous monitoring of vascular pressures (Bentley Trantek Model 500 transducers) and to obtain blood samples. Intravenous fluids were administered as needed to maintain a constant central venous pressure.

The following were measured and recorded: heart rate (HR), mean arterial pressure (MAP), arterial blood gas tensions, plasma renin activity (PRA) by radioimmunoassay (New England Nuclear, N. Billerica, ME), and epinephrine (E), norepinephrine (N), and dopamine (D) levels determined by high-performance liquid chromatography and electrochemical detection assay using the method of Moyer et al. (25). The above measurements were made: 1) when patients were awake in the operating room; 2) after induction of N_2O-O_2-fentanyl anesthesia; 3) after intra-abdominal surgery had begun; 4) after MAP was lowered to 60 mm Hg for 20 min with SNP infusion; 5) 20 minutes after esmolol infusion at each of the following rates: 200, 300, and 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with SNP doses reduced to maintain MAP at 60 mm Hg; and 6) at the termination of operation, after both SNP and esmolol had been terminated simultaneously.

The effects of esmolol on SNP requirement, PRA, and HR were evaluated statistically using growth curve analysis. The linear growth curve models of Rao (26), which relate the mean growth of the observed data points to a polynomial function of the esmolol dose, were fitted to the data. A least-squares procedure was then used to estimate the parameters of the growth curve models. For SNP dose requirement and plasma renin activity, simple growth curve models were fitted to the data; for heart rate, a quadratic model was necessary. Data obtained before and after esmolol infusion were compared using Student's two-tailed paired *t*-test. $P < 0.05$ was regarded as representing statistical significance.

Results

The results of the study are summarized in Fig. 1–4 and Table 1. SNP-induced hypotension during surgery with a fentanyl-O_2-N_2O-pancuronium anesthetic technique was associated with significant increases in HR, PRA, N, and D levels and a significant decrease in PaO_2. After 20 min of esmolol infusion at 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$, there was a significant reduction in SNP dose requirement and concomitant significant reductions in HR and PRA below values obtained just before esmolol was begun. After 20 min of esmolol infusion at 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (40 min after esmolol

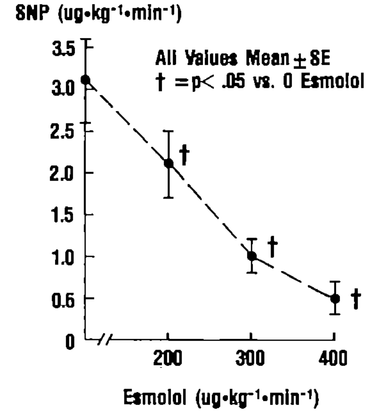


Figure 2. Dose of sodium nitroprusside required to maintain mean arterial pressure at 60 mm Hg, without and with concomitant esmolol infusion.

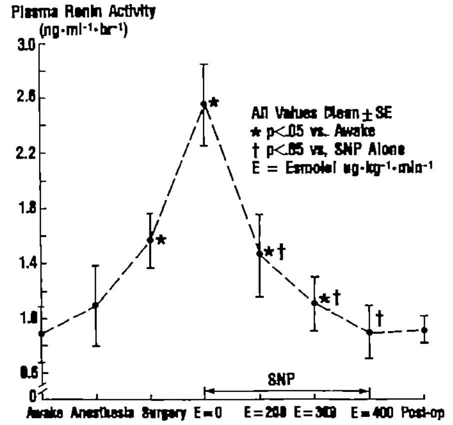


Figure 4. Plasma renin activity throughout the study, showing increases in response to surgery and SNP-infusion followed by significant reductions after esmolol infusion began.

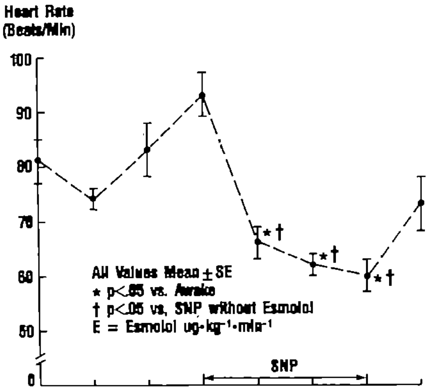


Figure 3. Heart rate responses to induction of anesthesia, surgical stimulation, SNP-induced hypotension and subsequent esmolol infusion.

was begun), SNP dose requirement was further reduced, PaO_2 was significantly increased and PRA, N, and E levels were all significantly less than values observed during SNP infusion without esmolol. In 4 patients, when esmolol infusion was increased to 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$, SNP was no longer required to maintain MAP at 60 mm Hg, and in one patient (age = 75 years) esmolol had to be terminated due to a heart rate below 50 bpm. With an esmolol infusion rate of 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$, PaO_2, PRA, N, and E values were not significantly different from those obtained when the patients were awake. At the end of the operation, there was no evidence of rebound hypertension and HR, BP, PRA, PaO_2 were not significantly different from the corresponding preoperative values; only E levels remained significantly elevated.

Discussion

Beta-adrenergic blockade is well-established as a simple and safe technique for minimizing SNP dose-requirement (19–21), improving oxygenation during SNP infusion (19), and preventing rebound hypertension at the completion of SNP administration (20). Beta-blockade is known to have multiple effects during SNP-induced hypotension. First, it decreases heart rate by inhibiting adrenergic receptors responsible for the compensatory tachycardia usually seen during hypotension. Second, it decreases myocardial contractility, thus augmenting the hypotension induced by peripheral vasodilation and also preventing the excessively high cardiac output hypothesized as being responsible for deterioration in oxygenation during SNP infusion (12,13). Finally, beta-blockade inhibits the release of renin from the renal juxtaglomerular apparatus of the kidney (19). It is the activation of the renin-angiotensin system and the production of high levels of the vasoconstrictor, angiotensin II, that is thought to be primarily responsible for resistance to the effects of SNP and for the rebound hypertension that may occur when SNP is discontinued (20).

Despite the advantages of beta-blockade for potentiation of SNP-induced intraoperative hypotension, until recently there has been no beta-adrenergic blocking agent with a time-action curve similar to that of SNP. Thus, there has been concern that residual beta-blockade in the postoperative period might mask tachycardia indicative of either hypovolemia or hypoxemia. Since esmolol has both a rapid onset and a brief half-life, it would appear to be a logical adjuvant for SNP. The data presented here indicate that esmolol, in a dose range of 200–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$, is capable of quickly potentiating the hypotensive effects of SNP, both through its negative chronotropic effect on the cardiovascular system and by preventing release of renin. While we did not measure cardiac output or other indices of hemodynamic

Table 1. Changes in Arterial Catecholamine Levels and Blood Gas Tensions Throughout the Study

	EPI	NOR-EPI	Dopamine	pH	$PaCO_2$	PO_2
Awake	63 ± 8	330 ± 31	14 ± 7	—	—	—
Anesthesia	10 ± 4*	136 ± 21*	4 ± 3	7.45 ± 0.01†	37 ± 2	197 ± 14†
Surgery	65 ± 21	352 ± 43	30 ± 8*	7.42 ± 0.01	39 ± 2	183 ± 14†
SNP without E	74 ± 20	615 ± 105*	72 ± 15*	7.41 ± 0.01	38 ± 1	141 ± 18
SNP + E = 200	56 ± 13	398 ± 48	85 ± 19*	7.42 ± 0.01	37 ± 1	144 ± 17
SNP + E = 300	38 ± 8†	356 ± 46†	57 ± 10*	7.39 ± 0.02	38 ± 2	162 ± 16†
SNP + E = 400	71 ± 27	398 ± 69	198 ± 145	7.40 ± 0.02	36 ± 1	172 ± 14†
Recovery room	460 ± 98*	629 ± 146	331 ± 282	7.33 ± 0.01†	45 ± 2†	175 ± 28

SNP + E, sodium nitroprusside plus esmolol in $\mu g \cdot kg^{-1} \cdot min^{-1}$.
All Values = Mean ± SEM.
*, $P < .05$ vs Awake.
†, $P < .05$ vs SNP without E.
EPI, Epinephrine; NOR-EPI, Nor-epinephrine.

performance, esmolol has been shown to depress both cardiac output and stroke volume during general anesthesia in man (27,28), and we have no reason to doubt that these effects also occurred during the present study, although the usual response might have been modified by concomitant administration of SNP.

Esmolol has also been investigated as the sole agent for inducing controlled hypotension. At a dose of 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$, esmolol does not reliably produce a 15% reduction in blood pressure, even in the presence of isoflurane anesthesia (29,30). As the present study demonstrates, it was possible to induce a MAP of 60 mm Hg in only 4 of 10 patients with an esmolol dose of 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Furthermore, esmolol had to be terminated in one of these patients because of an excessively slow heart rate (<50 beats/min). It is because of the difficulty in reliably inducing hypotension with esmolol alone that a combined SNP-esmolol technique is intuitively attractive.

Since esmolol infusion in this study was not randomized, these data should not be considered an exact description of the dose-response interaction between SNP and esmolol. It is possible that some of the effects of the 300 and 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rates were caused by the duration of esmolol infusion or ongoing surgical events rather than being induced by the dose of esmolol administered. However, since the time of onset of esmolol is approximately 2 minutes and its elimination half-life is only 9 min (31), we believe that the data recorded after 20 min of esmolol infusion at 300 or 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$ are reasonably close to the steady-state relationship that would have been determined if a non-sequential dosing protocol had been followed. Since none of these patients had significant blood loss during the one-hour study period, we doubt that our results were biased by always infusing esmolol in the same dose sequence. From a practical point of view, we felt that it was not in the patients' best interest to risk infusing esmolol at 400 $\mu g \cdot kg^{-1} \cdot min^{-1}$ while the mean blood pressure had already been lowered to 60 mm Hg.

The time-action curve of the effect of esmolol on the adrenergic and renin-angiotensin systems is not known. It is, therefore, more plausible that our sequential dosing scheme introduced bias in interpreting the responses of plasma catecholamines levels and PRA to the different rates of infusion of esmolol. While our data suggest that 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is an optimal dose for blunting these responses, it might be that 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ would have been equally effective if it had been continued for 40 minutes. Previous work with propranolol indicated a 40-minute time lag between administration of propranolol and a significant reduction in PRA (19). Given the rapid onset and termination of action of esmolol, it should be reasonably easy to define the time-action curve for the effects of esmolol on these humoral functions in subsequent studies.

In conclusion, we found a profound potentiation of hypotensive action of SNP when esmolol is administered simultaneously. The effect of esmolol is mediated by a direct chronotropic action on the heart as well as by inhibition of the renin-angiotensin and catecholamine responses to SNP-induced hypotension. It is likely that a negative inotropic effect of esmolol may be contributory, but this was not studied directly. The similar pharmacokinetic and pharmacodynamic properties of SNP and esmolol make this combination of agents an easy and attractive technique for inducing controlled intraoperative hypotension.

References

1. Amaranath L, Kellermeyer WF. Tachyphylaxis to sodium nitroprusside. Anesthesiology 1976;44:345–8.
2. Cottrell JE, Patel K, Casthely P, Klein A, Turndorf H. Nitroprusside tachyphylaxis without acidosis. Anesthesiology 1978; 49:141–2.

3. Bedford RF, Berry FA Jr, Longnecker DL. Impact of propranolol on hemodynamic response and blood cyanide levels during nitroprusside infusion: a prospective study in anesthetized man. Anesth Analg 1979;58:466–9.
4. Greiss L, Tremblay NAG, Davies DW. The toxicity of sodium nitroprusside. Canad Anaesth Soc J 1976;23:480–5.
5. Mac Rae WR, Owen M. Severe metabolic acidosis following hypotension induced with sodium nitroprusside. Br J Anaesth 1974;46:795–7.
6. Michenfelder JD. Cyanide release from sodium nitroprusside in the dog. Anesthesiology 1977;46:196–201.
7. McDowall DG, Keaney NP, Turner JM, Lane JR, Okuda Y. The toxicity of sodium nitroprusside. Br J Anaesth 1974;46:327–32.
8. Vesey CJ, Cole PL, Simpson PJ. Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. Br J Anaesth 1976;48:651–60.
9. Michenfelder JD, Tinker JH. Cyanide toxicity and thiosulfate protection during chronic administration of sodium nitroprusside in the dog: correlation with a human case. Anesthesiology 1977;47:441–8.
10. Posner MA, Rodkey FL, Tobey RE. Nitroprusside-induced cyanide poisoning: antidotal effect of hydroxocobalomin. Anesthesiology 1976;44:330–5.
11. Cottrell JE, Casthely P, Brodie JD, Patel K, Klein A, Turndorf H. Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalomin. N Engl J Med 1978;298:809–11.
12. Benumof JL. Hypoxic pulmonary vasoconstriction and infusion of sodium nitroprusside. Anesthesiology 1979;50:481–3.
13. Cheney FW, Colley PS. The effect of cardiac output on arterial blood oxygenation. Anesthesiology 1980;51:496–503.
14. Khambatta HJ, Stone JG, Khan E. Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 1979;51:127–30.
15. Bedford RF. Sodium nitroprusside: hemodynamic dose-response during enflurane and morphine anesthesia. Anesth Analg 1979;58:174–8.
16. Bedford RF. Increasing halothane concentrations reduce nitroprusside dose requirement. Anesth Analg 1978;57:457–62.
17. Jennings GL, Gelman JS, Stockigt JR, Korner PI. Accentuation of hypotensive effect of SNP in man after captopril. Clin Sci 1981;61:521–6.
18. Woodside J Jr, Garner L, Bedford RF, Sussman MD, Miller ED, Longnecker DE, Epstein RM. Captopril reduces the dose requirement for sodium nitroprusside induced hypotension. Anesthesiology 1984;60:413–7.
19. Marshall WK, Bedford RF, Arnold WP, et al. Effects of propranolol on the cardiovascular and renin-angiotensin systems during hypotension produced by sodium nitroprusside in man. Anesthesiology 1981;55:277–80.
20. Khambatta HJ, Stone JG, Khan E. Propranolol alters renin release during nitroprusside-induced hypotension and prevents hypertension on discontinuation of nitroprusside. Anesth Analg 1981;60:569–73.
21. Pettinger WA, Keeton K. Altered renin release and propranolol potentiation of vasodilatory drug hypotension. J Clin Invest 1975;55:236–43.
22. Gray RJ, Bateman TM, Czer LSC, Conklin C, Matloff JM. Comparison of esmolol and nitroprusside for acute post-cardiac surgical hypertension. Am J Cardiol 1987;59:887–91.
23. Abrams J, Allen J, Anderson S. Efficacy and safety of esmolol vs propranolol in the treatment of supraventricular tachyarrhythmias: a multicenter double blind clinical trial. Am Heart J 1986;111:42–8.
24. Sheppard D, DiStefano S, Byrd RC. Effects of esmolol on airway function in the patients with asthma. J Clin Pharmacol 1986;26:169.
25. Moyer TP, Jiang N, Tyee GM, Sheps SG. Analysis for urinary catecholamines by liquid chromatography with amperometric detection: methodology and clinical interpretation of results. Clin Chem 1979;25:256– 63.
26. Rao CR. Some problems involving linear hypotheses in multivariate analysis. Biometrika 1959;46:49–58.
27. Newsome LR, Roth JV, Hug CC, Nagle DM. Esmolol attenuates hemodyamic responses to intubation and surgical stimulation during open heart surgery. Anesthesiology 1985;63:A62.
28. Menkhaus PG, Reves JG, Kissin I, Alvis JM, Govier AV, Samuelson PN, Lell WA, Henling CE. Bradley E. Cardiovascular effects of esmolol in anesthetized humans. Anesth Analg 1985;64:327–34.
29. Ornstein E, Matteo RS, Schwartz AE. The use of esmolol for deliberate hypotension. Anesthesiology 1986;65:A575.
30. Ornstein E, Matteo RS, Weinstein JA, Schwartz AE. A randomized controlled trial of esmolol for deliberate hypotension. Anesthesiology 1987;67:A423.
31. Sum CY, Yacobi A, Kartzinel R, Stampfli H, Davis CS, Lai C. Kinetics of esmolol, an ultrashort-acting beta blocker, and of its major metabolite. Clin Pharmacol Ther 1983;34:427–34.

Early Postoperative Arterial Oxygen Desaturation

Determining Factors and Response to Oxygen Therapy

Jaume Canet, MD, Montserrat Ricos, MD, and Fernando Vidal, MD

CANET J, RICOS M, VIDAL F. Early postoperative arterial desaturation. Determining factors and response to oxygen therapy. Anesth Analg 1989;69:207–12.

Oxygen arterial saturation (Sa_{O_2}) was measured with a pulse oximeter in 209 patients after elective surgery. Measurements were made upon arrival in the recovery room (RR) and 1 hr later. On each occasion, the patients randomly and alternately breathed—for 10 min at a time—room air or 35% O_2. Factors that might influence the incidence of postoperative hypoxemia were analyzed. After breathing room air for 10 min after arrival in the RR, the mean Sa_{O_2} was 90.7 ± 3.9% (±SD). Twenty min after and 1 hr after arrival in the RR, mean Sa_{O_2} increased significantly to 92.4 ± 3.5% ($P < 0.001$) and 93.2 ± 3.0% ($P < 0.001$), respectively. Postoperative hypoxemia ($Sa_{O_2} \leq 90\%$) after breathing room air for 10 min at 10 min, 20 min, and 1 hr after arrival in the RR occurred in 43.8%, 26.9%, and 16.9% of the patients, respectively. Breathing 35% O_2 for 10 min 10 min after arrival in the RR, as well as 20 min and 1 hr after arrival, significantly increased Sa_{O_2} above the Sa_{O_2} level after breathing room air by 5.7% ($P < 0.001$), 4.3% ($P < 0.001$), and 4.0% ($P < 0.001$), respectively. A significant multiple correlation was found between low Sa_{O_2} levels while breathing room air on arrival in the RR and fentanyl dose, age, and concentration of halothane used intraoperatively ($R = 0.46$; $P < 0.001$). The data demonstrate that, in the first minutes in the RR, there is a high incidence of hypoxemia, that administration of 35% O_2 relieves arterial desaturation, and that the type of anesthetic and age are the main factors influencing early postoperative hypoxemia.

Key Words: HYPOXIA—postoperative. OXYGEN—therapeutic.

Early postoperative hypoxemia as a postanesthetic complication often appears at the end of an operation and may linger through the first postoperative hours. It is the result of changes in respiratory function during anesthesia, especially increases in pulmonary shunting and dead space. In addition, posthyperventilation hypoventilation and the persistence of ventilatory depression produced by anesthetics and muscular relaxants aggravate hypoxemia (1,2).

The availability of pulse oximetry (3) has made it possible to make continuous measurements of arterial oxygen saturation (Sa_{O_2}) intra- and postoperatively. In the last few years, studies have analyzed arterial oxygen desaturation during anesthesia (4–6), transfer to the recovery room (RR) (7,8) and immediate postoperative period in children (9,10). Sa_{O_2} in the early period of anesthetic recovery, however, has not been extensively and continuously measured using pulse oximetry. Although routine administration of oxygen during the postanesthetic period is widely accepted, the benefit of this therapy, quantitated in terms of changes in Sa_{O_2}, has not been reported.

The purpose of this study was to measure Sa_{O_2} changes with a pulse oximeter during the first postoperative hour in a large sample of nonhomogeneous patients; at the same time, we quantified the effect of oxygen therapy on Sa_{O_2} and analyzed factors that reduce Sa_{O_2}.

Methods

Two hundred-nine patients scheduled for elective surgery participated in the study. Institutional approval and individual patient consents were obtained. Table 1 lists the general characteristics of the patients. We included patients regardless of sex, age, type of surgery and anesthesia, or physical status. Patients who were not breathing spontaneously upon

---

Received from the Servei d'Anestesiología i Reanimació, Hospital "Germans Trias i Pujol," Badalona, Barcelona, Spain. Accepted for publication March 15, 1989.

Address correspondence to Dr. Canet, Servei d'Anestesiología i Reanimació, Hospital "Germans Trias i Pujol," 08916 Badalona, Barcelona, Spain.

©1989 by the International Anesthesia Research Society

Table 1. General Data

No. of patients	209
Sex (male/female)	119/90
Age (yr)	46 ± 20 (3–86)
Weight (kg)	63 ± 14 (15–98)
Height (cm)	159 ± 13 (95–185)
Body Mass Index (kg × m^{-2})	24 ± 4 (15–36)
ASA physical status (%)	
I	43%
II	39%
III	18%

Data are ±SD; ranges are expressed in parentheses.

arrival in the RR were excluded. The transfer time from the operating room to the RR was always <30 sec. Measurement of Sa_{O_2} began on arrival in the RR.

Sa_{O_2} was measured with the ear probe of a pulse oximeter Biox 3700 (Ohmeda, Boulder, CO). When the signal of the pulse wave was unsatisfactory due to faulty peripheral perfusion or jaundice, the patient was excluded. When O_2 was given, a Venturi mask was used.

On arrival in the RR the patients were randomly divided into two groups. The patients of the first group (IA) breathed room air for 10 min and then were immediately given 35% O_2 for 10 min more. The patients in the second group (IO) underwent reverse procedure: they breathed 35% O_2 for the first 10 min and room air for the next 10 min. Measurements of Sa_{O_2} were made at the end of each 10 min period. At 1 hr, the number of patients was 207 because two children had been discharged. These 207 patients were once again randomly redivided into two new groups (IIA and IIO) and they followed the same procedure of alternately breathing room air or 35% O_2. At the end of each 10-min period, the Sa_{O_2} once again was measured with the pulse oximeter. During the rest of the stay in the RR all patients breathed 35% O_2 and vital signs were measured every 15 min.

All data are given as mean ± SD. We used a paired *t*-test to determine the statistical significance of differences of Sa_{O_2} when different situations within a single group of patients were analyzed and a two-sample *t*-test when different groups were compared. Patients were categorized each time Sa_{O_2} was measured on the basis of Sa_{O_2} levels as being nonhypoxemic ($Sa_{O_2} \geq 91\%$), hypoxemic ($Sa_{O_2} = 86\%–90\%$) or severely hypoxemic ($Sa_{O_2} \leq 85\%$), the number of patients in each category then being analyzed for statistically significant differences using a χ^2-test. Comparisons between Sa_{O_2} levels were made with a two-sample *t*-test with the patients separated according to sex; type of anesthesia used (both general and regional anesthesia); site of operation, there being both central (intrathoracic or intraabdominal), as well as peripheral (head, neck, limbs, or abdominal or chest wall); and preexisting pulmonary disease (i.e., whether the patient had a clinical history of chronic obstructive disease or asthma [11]). A stepwise multiple linear regression was made between the Sa_{O_2} after breathing room air on arrival in the RR as a dependent variable, and the rest of the variables. We looked for a regression model fitted to the variables to predict the Sa_{O_2} breathing room air on arrival. A *P* value <0.05 was considered statistically significant.

Results

Table 2 presents the mean postoperative Sa_{O_2} levels on arrival in the RR and 1 hr later both after breathing room air and after breathing 35% O_2 for patients randomly assigned to breathe either room air (A) or 35% O_2 (O) first. A statistically significant difference in Sa_{O_2} after breathing room air on arrival in the RR was found between the patients initially breathing air (A) and those breathing 35% O_2 (O). The mean for the A group was 90.7 ± 3.9% and for the O group 92.4 ± 3.5%. This difference represents a significant increase of 1.7% in Sa_{O_2} breathing room air between 10 and 20 min after arrival in the RR. The magnitude of this same difference was not great enough to be statistically significant 1 hr later. The Sa_{O_2} in patients breathing room air 1 hr after arrival in the RR increased to a mean of 93.0 ± 3.0% in both groups, a level significantly above the level of Sa_{O_2} observed when room air was breathed when first admitted to the RR.

In all instances statistically significant increases in Sa_{O_2} were produced by breathing 35% O_2. The increase averaged 5.7% in patients who breathed room air for the first 10 min after arrival in the RR and 4.3% in patients who breathed room air between 10 and 20 min later. One hour later the mean increase when patients breathed 35% O_2 was of 4.0%, with no significant difference between the two groups.

Table 3 presents the number and percentage of patients according to levels of hypoxemia. The results are grouped, as in Table 2, for each of the four measurements of Sa_{O_2} and for the random groups. We found a statistically significant difference in the distribution of hypoxemic levels between the A and O groups after breathing room air on arrival in the RR. Hypoxemia and severe hypoxemia occurred in 43.8% and 11.4% of the sample, respectively, 10 min after arrival in the RR, and in 26.9% and 3.8% at 20 min.

The general characteristics, duration of operation and Sa_{O_2} with each measurement are broken down in

Table 2. Postoperative Arterial Oxygen Saturations in the Recovery Room

On arrival in RR			After 1 hr in RR		
Group	Room air	35% oxygen	Group	Room air	35% oxygen
IA (N = 105)	90.7 ± 3.9	96.4 ± 2.4^b	IIA (N = 103)	93.0 ± 2.8^c	96.9 ± 2.2^b
	^{a}				
IO (N = 104)	92.4 ± 3.5	96.7 ± 2.1^b	IIO (N = 104)	93.4 ± 3.1^c	97.4 ± 2.0^{bd}

IA and IIA are patients who first breathed room air for 10 min and then 35% O_2 for 10 min. IO and IIO are patients that first breathed 35% O_2 for 10 min and then room air for 10 min.

[a] Statistically significant difference in Sao_2 between groups IA and IO ($P < 0.001$; two-sample *t*-test).

[b] Statistically significant difference in Sao_2 between room air and 35% O_2 breathing within the single groups (IA, IO, IIA, IIO) ($P < 0.001$; paired *t*-test).

[c] Statistically significant difference in Sao_2 between groups IA and IIA and groups IO and IIO after breathing room air ($P < 0.001$; two-sample *t*-test).

[d] Statistically significant difference in Sao_2 between groups IO and IIO after breathing 35% O_2 ($P < 0.001$; two-sample *t*-test).

Table 3. Number and Percentage of Patients Categorized by Levels of Arterial Saturation

	On arrival in RR			After 1 hr in RR		
Sao_2 (%)	Group	Room air	35% oxygen	Group	Room air	35% oxygen
	IA (N = 105)			IIA (N = 103)		
≥91		59 (56.2)	103 (98.1)		86 (83.5)	102 (99.0)
90–86		34 (32.4)	2 (1.9)		14 (13.6)	1 (1.0)
≤85		12 (11.4)	0		3 (2.9)	0
		^{a}				
	IO (N = 104)			IIO (N = 104)		
≥91		76 (73.1)	103 (99.0)		86 (82.7)	104 (100)
90–86		24 (23.1)	1 (1.0)		16 (15.4)	0
≤85		4 (3.8)	0		2 (1.9)	0

Groups are as in Table 2. Values express numbers of patients; percentages are expressed in parentheses.

[a] Statistically significant difference between groups IA and IO ($P < 0.01$; χ^2-test)

Table 4. General Data and Saturations by Factors

	Sex		Type of Anesthesia		Site of Operation		Preexisting Pulmonary Disease	
	Male	Female	General	Regional	Central	Peripheral	Yes	No
Number of patients	119	90	150	56	65	144	65	144
Sex (male/female)	—	—	79/71^a	39/17	29/36^a	90/54	52/13^c	67/77
Age (yr)	46 ± 21	47 ± 18	42 ± 19^c	58 ± 16	50 ± 17^a	44 ± 21	56 ± 16^c	42 ± 20
Weight (kg)	63 ± 17	62 ± 11	61 ± 16^a	66 ± 10	63 ± 12	62 ± 16	65 ± 12	61 ± 15
Height (cm)	161 ± 17^b	156 ± 7	158 ± 15	161 ± 8	159 ± 9	159 ± 15	162 ± 10	157 ± 15
BMI (kg × m^{-2})	23.6 ± 4.3^b	25.4 ± 4.1	24.0 ± 4.4	25.3 ± 4.1	24.5 ± 4.2	24.3 ± 4.4	24.4 ± 3.8	24.3 ± 4.5
Time of surgery (min)	91 ± 44	99 ± 40	99 ± 43^a	83 ± 39	109 ± 38^c	88 ± 43	93 ± 43	95 ± 42
Sao_2								
Air on arrival	91.9 ± 3.7^a	90.9 ± 3.7	90.6 ± 3.7^c	93.9 ± 2.6	90.4 ± 3.4^b	92.0 ± 3.8	91.1 ± 3.8	91.6 ± 3.7
O_2 on arrival	96.7 ± 2.3	96.4 ± 2.2	96.3 ± 2.2^b	97.3 ± 2.2	96.2 ± 2.0	96.7 ± 2.4	96.3 ± 2.5	96.7 ± 2.2
Air at 1 hr	93.7 ± 2.8^a	92.7 ± 3.2	92.6 ± 3.0^c	94.9 ± 2.3	92.1 ± 3.1^c	93.8 ± 2.8	92.9 ± 3.0	93.4 ± 3.0
O_2 at 1 hr	97.3 ± 2.1	97.0 ± 1.9	97.0 ± 2.0^a	97.7 ± 2.0	96.6 ± 1.8^b	97.5 ± 2.1	97.0 ± 2.3	97.3 ± 1.9

Values are expressed as mean ± SD. Abbreviation: BMI body, mass index.

[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$ (two-sample *t*-test)

Table 4 into four factors: sex, type of anesthesia, site of operation, and preexisting pulmonary disease. The Sao_2 levels in this table represent the means of the entire sample. The differences in Sao_2 depending upon whether room air or 35% O_2 was being breathed were greatest in comparisons between patients given general anesthesia and patients given regional anesthesia. The patients with preexisting pulmonary disease, when compared with patients with no such clinical history, did not show statistically significant differences in Sao_2 in any of the situations in which Sao_2 was measured.

A stepwise multiple linear correlation produced a multiple correlation coefficient of R = 0.46 ($P < 0.001$)

between the Sa_{O_2} breathing room air on arrival in the RR as a dependent variable and three variables: fentanyl dose, age, and halothane concentration. The equation obtained was $Sa_{O_2} = 96.16 - 4.34$ fentanyl dose (mg) $- 0.05$ age (yr) $- 2.24$ halothane concentration (%). The standardized regression coefficients for each of the three independent variables in the equation were $R = -0.402$ ($P < 0.001$), $R = -0.258$ ($P < 0.001$), $R = -0.257$ ($P < 0.001$), respectively.

Discussion

Anesthesia is associated with ventilatory changes that start with the administration of premedication (12), and may last some days after the surgical procedure (13). Hypoxemia is the most obvious result of these changes. Many explanations for postanesthetic hypoxemia have been proposed (14), with perhaps venous admixture and pulmonary shunting being today the ones most studied (2,15). The early postoperative period is one of the times when patients are most apt to develop the greatest degree of arterial desaturation. This is because of continuing respiratory abnormalities caused by the anesthesia itself, and also because during the early postoperative period patients previously artificially ventilated, and often hyperventilated, are beginning to reassume spontaneous ventilation (14).

Conway and Payne (16) found an Sa_{O_2} of 92.1% in the immediate postoperative period of 15 healthy patients. Motoyama and Glazener (9) found an Sa_{O_2} of 93% in 97 children on arrival in the RR, with a significant increase to 94.1% 5–15 min later. In our study (see Table 2), the Sa_{O_2} level while breathing room air increased significantly from 90.7% at 10 min after arrival in the RR to 92.4% 20 min after arrival in the RR, and to 93.2% at somewhat >1 hr later. The marked increase of Sa_{O_2} during the first minutes, which later became moderate, is due to the rapid disappearance of the depressant effects of anesthetic drugs and posthyperventilation hypoventilation (2). Although it has been considered that early hypoxemia lasts about 2 hr after the surgical procedure (1), the first 20 minutes of the postoperative period seem to be most critical.

The incidence of immediate postoperative hypoxemia reported in different studies varies considerably. Tyler et al. (7) found hypoxemia and severe hypoxemia in 35% and 12% of their adult ASA physical status I and II patients being transferred from the operating room to the RR. Hypoxemia was present in 29% of adult patients undergoing peripheral surgery on arrival in the RR (17). In children the incidence of hypoxemia is lower. Vijayakumar et al. (10) found hypoxemia in an average of 28% of children being transferred to the RR but that this condition depended in part on the concentration of oxygen they breathed before leaving the operating room. In the same way, Pullerits et al. (8) also found hypoxemia and severe hypoxemia in 28% and 12.7%, respectively, of children during transfer to the RR. In our study (see Table 3), we found hypoxemia and severe hypoxemia in 43.8% and 11.4%, respectively, of patients that breathed room air during the first 10 min after arrival in the RR. These values are higher than the values obtained in the articles cited above. We consider that is due to the heterogeneity of our sample, which included a goodly percentage of ASA physical status III patients and patients who underwent major "central" operations. However, hypoxemia and severe hypoxemia decreased to 26.9% and 3.8%, respectively, among the patients who breathed room air between 10 and 20 min after their arrival in the RR. One hour later, these values went down further to 16.9% and 2.4%, respectively. These findings strongly suggest that the first 20 min after the operation represent the critical time to watch for the appearance of hypoxemia.

The positive effect that oxygen therapy has on hypoxemia has been widely accepted (18). Our purpose was to quantify the increase in Sa_{O_2} during the early postoperative period. We chose a 35% O_2 concentration because it has been clearly demonstrated that higher concentrations are no more effective in preventing hypoxemia (18). Sa_{O_2} on the patients' arrival in the RR when breathing 35% O_2 for 10 min was 96.6%, without significant differences depending upon whether 35% O_2 or room air was first breathed. In the patients given air first, the increase of Sa_{O_2} after breathing 35% O_2 for 10 min was 5.7%, and in patients breathing 35% O_2 first the increase after 10 min averaged 4.3% above the levels of Sa_{O_2} breathing room air. Moreover, hypoxemia persisted in only three patients. One hour later, Sa_{O_2} after breathing 35% O_2 increased to 97.2%, a 4.0% increase when compared to Sa_{O_2} after 10 min breathing air after 1 hr in the RR, at which time when only one patient developed hypoxemia. Conway and Payne (18) found an increase in Sa_{O_2} of 5.3% when they provided patients with approximately 39% O_2 through a non-Venturi mask. Our study demonstrates that an oxygen concentration of 35% is effective in reducing hypoxemia in a general population of patients during the early postoperative period. In children, oxygen therapy is of special importance because in them postanesthetic recovery scores do not correlate with Sa_{O_2} (19).

Our study included a heterogeneous sample of patients in order to enable us to analyze the factors associated with early postoperative hypoxemia. A simple linear correlation analysis may be altered by interrelations among different factors, and for this reason we decided to make a stepwise multiple regression analysis. This analysis employs a tolerance test to look for variables which might enter into a predictable equation (20). Only three variables were found to be predictably related to oxygen desaturation, namely fentanyl dose, age, and halothane concentration.

Of these three variables, age has been the most studied. Nunn (21) found significant correlation between age and postoperative Pa_{O_2}. This correlation seems to be due to the relationships between age and the mismatching of ventilation to perfusion and age-related increases in closing volume (22), as reflected in normal decreases in Pa_{O_2} with age (2).

In our study we analyzed the effects of the type of anesthesia on early postoperative hypoxemia. We found a clear relationship between fentanyl dose and intraoperative halothane concentration and postoperative hypoxemia using multiple correlation analysis. In addition, as shown in Table 4, Sa_{O_2} was always higher in patients that had regional anesthesia. Furthermore, these patients were older than patients given general anesthesia. Since age is a significant determinant of postoperative Sa_{O_2}, if the ages had been more similar in the patients given regional and general anesthesia we might predict that the differences in Sa_{O_2} would have been greater. Other authors have found no differences in arterial blood gas tensions postoperatively in patients having regional or general anesthesia, perhaps because these studies were performed in carefully selected groups (23,24). Recently, McKay and Noble (5), studying a group of unselected patients, found that incidence of arterial desaturation during anesthetic induction, maintenance and emergence was significantly lower in patients having regional anesthesia. The effects of general anesthesia on pulmonary function (14) could be the reason for these differences in Sa_{O_2} in the early postoperative period in patients having general or regional anesthesia.

Sex has not been considered a determining factor in postoperative hypoxemia (2). We found Sa_{O_2} to be higher in males than in females at all observation times (see Table 4). The lower Sa_{O_2} levels in females may be due to the higher incidence of obesity. In connection with this, Tyler et al. (7) found a correlation between degree of obesity and the incidence of hypoxemia during the transfer of patients from the operating room to the RR.

Site of operation has been associated with postoperative hypoxemia (15), but not in the early postoperative period (22). We found that immediately postoperative Sa_{O_2} levels were significantly higher in patients who underwent peripheral operations than they were in patients who had thoracic or abdominal surgery (Table 4). In addition, we found that these Sa_{O_2} differences became greater one hour after arrival in the RR. We must point out that the majority of the thoracic or abdominal surgery patients were given general anesthesia, that the patients were older, and that these operations lasted longer. Type of anesthesia, age, and duration of surgery might be at least partly responsible for the differences observed.

Finally, our patients with preexisting respiratory disease had Sa_{O_2} levels that were not significantly different from those of patients without preexisting pulmonary disease, in spite of the fact that their mean age was higher. These results agree with other studies that found the effects of preexisting pulmonary disease to be more evident several hours after the end of surgery and to last for several days. The effects of preexisting pulmonary disease on arterial desaturation later in the postoperative period are intensified by pain that results in inadequate ventilation and secretory retention (2,13).

In summary, we found a mean Sa_{O_2} of 90.7% when patients were breathing room air during the first 10 min after arrival in the RR, with 43.8% of patients developing hypoxemia ($Sa_{O_2} \leq 90\%$). At 20 min and at 1 hr after arrival in the RR, Sa_{O_2}, while breathing room air increased to 92.4% and 93.2%, respectively, and hypoxemia developed in fewer patients (26.9% and 16.9%, respectively). When 35% O_2 was breathed, hypoxemia disappeared and the Sa_{O_2} on arrival in the RR increased to 5.7% above the level seen when patients breathed room air. The main factors related to early postoperative hypoxemia were type of anesthetic and age.

The authors wish to thank Mrs. Francisca Rodriguez for her technical assistance, Valentín Mazo, MD, for statistical analysis of the data, and Joaquín Sanchis, MD, for revision of the manuscript.

References

1. Craig DB. Postoperative recovery of pulmonary function. Anesth Analg 1981;60:46–52.
2. Marshall BE, Wyche MQ. Hypoxemia during and after anesthesia. Anesthesiology 1972;37:178–209.
3. Yelderman MF, New W. Evaluation of pulse oximetry. Anesthesiology 1983;59:349–52.
4. Brodsky JB, Shulman MS, Swan M, Mark JBD. Pulse oximetry during one-lung ventilation. Anesthesiology 1985;63:212–4.

5. McKay WPS, Noble WH. Critical incidents detected by pulse oximetry during anaesthesia. Can J Anaesth 1988;35:265–9.
6. Canet J, Montero A, Llorente C, Bassons J, Vidal F. Saturación arterial de oxígeno durante la inducción anestésica y la intubación orotraqueal. Rev Esp Anestesiol Reanim 1988;35:123–6.
7. Tyler IL, Tantisira B, Winter PM, Motoyama EK. Continuous monitoring of arterial oxygen saturation with pulse oximetry during transfer to the recovery room. Anesth Analg 1985; 64:1108–12.
8. Pullerits J, Burrows FA, Roy WL. Arterial desaturation in healthy children during transfer to the recovery room. Can J Anaesth 1987;34:470–3.
9. Motoyama EK, Glazener CH. Hypoxemia after general anesthesia in children. Anesth Analg 1986;65:267–72.
10. Vijayakumar HR, Metriyakool K, Jewell MR. Effects of 100% oxygen and a mixture of oxygen and air on oxygen saturation in the immediate postoperative period in children. Anesth Analg 1987;66:181–4.
11. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987;136:225–44.
12. Pierce JA, Garofalo ML. Preoperative medication and its effect on blood gases. JAMA 1965;194:487–90.
13. Palmer KNV, Gardiner AJS. Effect of partial gastrectomy on pulmonary physiology. Br Med J 1964;1:347–9.
14. Rehder K, Sessler AD, Marsh HM. General anesthesia and the lung. Am Rev Respir Dis 1975;112:541–63.
15. Diament ML, Palmer KNV. Venous/arterial pulmonary shunting as the principal cause of postoperative hypoxaemia. Lancet 1967;1:15–7.
16. Conway CM, Payne JP. Hypoxaemia associated with anaesthesia and controlled respiration. Lancet 1964;1:12–4.
17. Dale S, Rowbotham DJ, Nimmo W. Oxygen saturation in the recovery room. Br J Anaesth 1988;60:341P.
18. Conway CM, Payne JP. Post-operative hypoxaemia and oxygen therapy. Br Med J 1963;1:844–5.
19. Soliman IE, Patel RI, Ehrenpreis MB, Hannallah RS. Recovery scores do not correlate with postoperative hypoxemia in children. Anesth Analg 1988;67:53–6.
20. Dixon WJ, ed. BMDP Statistical Software. California: University of California Press, 1983:251–63.
21. Nunn JF. Influence of age and other factors on hypoxaemia in the postoperative period. Lancet 1965;2:466–8.
22. Kitamura H, Sawa T, Ikezono E. Postoperative hypoxemia: the contribution of age to the maldistribution of ventilation. Anesthesiology 1972;36:244–52.
23. Ravin MB. Comparison of spinal and general anesthesia for lower abdominal surgery in patients with chronic obstructive pulmonary disease. Anesthesiology 1971;35:319–22.
24. Hedenstierna G, Löfström J. Effect of anaesthesia on respiratory function after major lower extremity surgery. Acta Anaesthesiol Scand 1985;29:55–60.

ANESTH ANALG
1989;69:213–7

Midazolam-Alfentanil Synergism for Anesthetic Induction in Patients

H. R. Vinik, MD, E. L. Bradley Jr, PhD, and I. Kissin, MD, PhD

VINIK HR, BRADLEY EL, JR, KISSIN I.
Midazolam-alfentanil synergism for anesthetic induction in patients. Anesth Analg 1989;69:213–7.

The effect of midazolam on the induction dose-response curve for alfentanil was studied in nonpremedicated ASA physical status I or II patients. The response to the verbal command was used as an end point of anesthesia. Dose-response curves for midazolam, alfentanil, and their combination were determined with a probit procedure, and compared with algebraic (fractional) analysis of drug interaction. Interaction between midazolam and alfentanil was found to be synergistic (supraadditive). The results suggest that the use of this combination is advantageous not only because it helps to achieve different anesthetic goals with specific drugs (a benzodiazepine for unconsciousness and an opioid for blockade of the responses to noxious stimulation), but also because its components are complementary for unconsciousness.

Key Words: ANESTHETICS, INTRAVENOUS—midazolam, alfentanil. ANALGESICS, ALFENTANIL. HYPNOTICS, BENZODIAZEPINES, midazolam. INTERACTIONS, DRUGS—benzodiazepines, opioids. INDUCTION, ANESTHESIA—midazolam, alfentanil.

Several investigators (1,2) have reported enhancing the hypnotic effect of benzodiazepines with opioid drugs in patients undergoing surgery. An increase in the percent of patients anesthetized with alfentanil by the addition of diazepam also has been reported (3). Although benzodiazepine and opioid receptors are pharmacologically separate, these receptor systems may interact synergistically in the mediation of their effects (4). The finding that naloxone in a small dose (6 μg/kg) decreases the percent of patients rendered unconscious with diazepam agrees with this suggestion (5). The investigations with combined administration of benzodiazepines and opioids did not indicate whether the observed results reflect synergism or simple summation of the effects. The aim of the present study was to define the type of alfentanil-midazolam hypnotic interaction. These two agents were selected for the study because each has a rapid onset of action and a short elimination half-life in their respective group of pharmacologic agents (opioids and benzodiazepines) (6,7). As a result, alfentanil and midazolam have an important potential advantage for combined use in anesthesia.

Methods

Ninety ASA physical status I or II adult female patients scheduled for various gynecologic surgeries participated in the study, which was approved by the Institutional Human Investigation Committee. The patients were 18 to 60 years of age, with a weight range 45 to 90 kg. Patients who had received benzodiazepines or opioids within 1 month of the investigation were excluded from the study. None of the patients received any premedication.

Patients were randomly assigned to one of three groups: midazolam, alfentanil, or midazolam-alfentanil. Each group consisted of 30 patients divided into six subgroups of 5 patients, each with predetermined doses of drugs in each subgroup. The abolition of the ability to open (move) eyes on command was used as an end point of anesthesia. Absence of the response to two consecutive voice commands was regarded as a positive response. The study was designed in a double-blind manner.

The following predetermined doses of drugs were administered: in the midazolam group (mg/kg): 0.08, 0.10, 0.13, 0.18, 0.26, 0.35; in the alfentanil group

---

Received from the Department of Anesthesiology, School of Medicine, University of Alabama at Birmingham, UAB Station, Birmingham, AL. Accepted for publication January 13, 1989.

Address correspondence to Dr. Kissin, Department of Anesthesiology, School of Medicine, University of Alabama at Birmingham, UAB Station, Birmingham, AL 35294.

©1989 by the International Anesthesia Research Society

(mg/kg): 0.06, 0.08, 0.10, 0.12, 0.14, 0.18. In the midazolam-alfentanil group, midazolam was used in a fixed dose of 0.07 mg/kg and the alfentanil dose varied. As a result, the following doses were used (mg/kg): 0.07 and 0.02, 0.07 and 0.025, 0.07 and 0.030, 0.07 and 0.040, 0.07 and 0.050, 0.07 and 0.060 (midazolam and alfentanil, respectively). Doses of midazolam and alfentanil were expressed in terms of the salt. The dose ranges were selected on the basis of a preliminary study, the results of which are not included in the present report.

All drugs were injected intravenously in an upper extremity over 10 s into a rapidly flowing intravenous infusion via the port nearest the intravenous catheter. In the midazolam-alfentanil group, midazolam was injected first, followed 1 min later by alfentanil. The end point (unconsciousness) was determined 3 min after the first injection. In the midazolam group, 1 min after injection of midazolam, 10 ml of isotonic saline solution was injected, and 3 min after the first injection, the end point of anesthesia was checked. In the alfentanil group, isotonic saline solution was injected first, alfentanil was injected 1 min later, and the end point was determined 2 min after the injection of alfentanil. After determining the response to verbal command, all patients received additional anesthesia if needed to assure that anesthesia was adequate before starting the surgical procedure. Times between injections of drugs and determination of the end point were based on the times to peak effect for these agents: 3 min for midazolam (2) and 2 min for alfentanil (8). With combined drug administration, both drugs were injected so that synchronization of the peak effects would occur. These time intervals were selected on the basis of a preliminary study. No neuromuscular blocking agents were given before induction because there is an indication that they may reduce anesthetic requirement (9).

The percent of patients unable to respond to the command was converted into probit values, and plotted against logarithmic values for the respective doses. Dose-response curves and ED_{50} values were determined with the use of probit analysis (10). To define the type of interaction between alfentanil and midazolam, an algebraic (fractional) method of drug interaction analysis (at ED_{50} level) was used (11). The algebraic analysis was based on the expression of doses of alfentanil and midazolam components of the combination (Ac and Mc) as fractions of the doses of these drugs that produce the same effect when given separately (Ac/As and Mc/Ms). The sum of these fractional doses, as expressed by the following equation, indicates the type of interaction. It is equal to 1 with addition (summation), >1 in antagonism, and <1 in synergism (see example in Results).

Table 1. Characteristics of Patients

Variable	Groups Midazolam	 Alfentanil	 Midazolam-Alfentanil
Age (yr)	34 ± 8	37 ± 9	31 ± 4
Weight (kg)	65 ± 12	65 ± 12	65 ± 9
No. of patients (all female)	30	30	30

Data are reported as mean ± SD.

$$\frac{Ac}{As} + \frac{Mc}{Ms} \begin{matrix} = 1 \\ > 1 \\ < 1 \end{matrix}$$

A statistical test for additivity was performed in the following way. The logarithm of the fractional dose of alfentanil ($ED_{50}Ac/ED_{50}As$) was compared with the logarithm of the quantity: theoretical additive ratio of 1 minus the fractional dose of midazolam ($Mc/ED_{50}Ms$, where Mc is a fixed dose) denoted by log (1-fM). The logarithm of the fractional dose of alfentanil (denoted by logfA) can be expressed as the difference of the logarithm of $ED_{50}Ac$ (alfentanil dose when given in combination with midazolam) minus the logarithm of $ED_{50}As$ (alfentanil dose when given separately). The standard error of this difference (denoted by SED) was computed from the standard errors of the corresponding logarithm of ED_{50}s, obtained from individual probit analyses with the use of a method of propagation of error (12). A *t*-test was then computed in the standard fashion as $t = [\log(fA) - \log(1\text{-}fM)]/SED$ to provide a statistical test for additivity.

Results

The study groups were comparable with respect to age and weight (Table 1). The midazolam dose-response curve for induction of anesthesia is presented in Figure 1. The midazolam ED_{50} value obtained from this curve was 0.21 mg/kg (95% confidence limits, 0.15–0.50 mg/kg). Figure 2 represents the alfentanil dose-response curves for induction of anesthesia with and without the addition of midazolam 0.07 mg/kg (one-third of the midazolam ED_{50} value). The addition of midazolam markedly shifted the alfentanil dose-response curve to the left along the dose axis. The alfentanil ED_{50} value was 0.134 mg/kg (range 0.110–0.193), which decreased to 0.028 mg/kg (range 0.018–0.036) with the addition of midazolam. A comparison of the combined and sin-

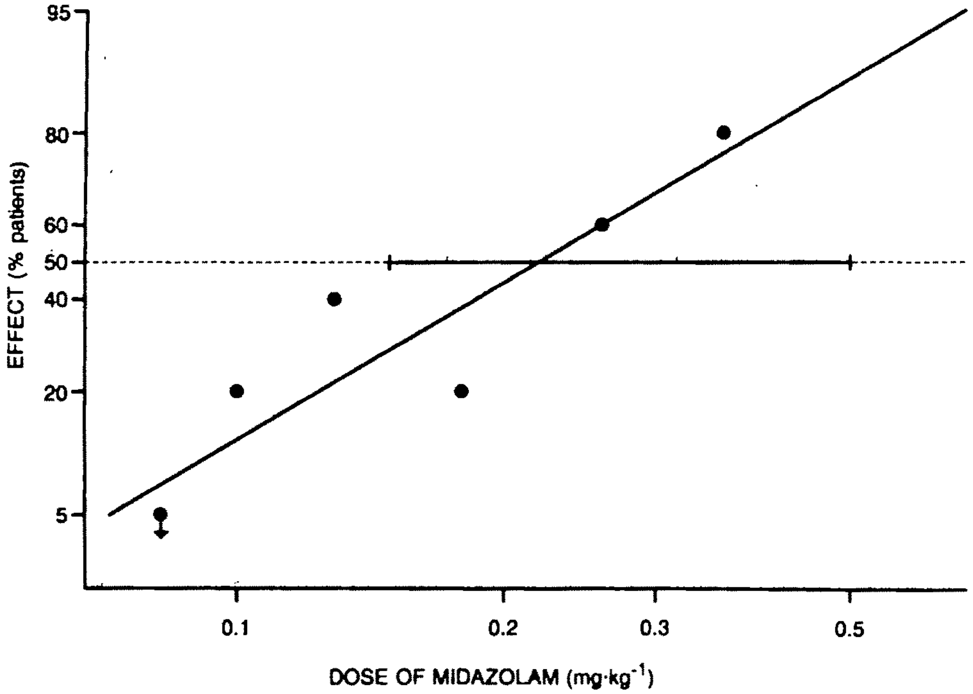


Figure 1. Midazolam dose-response curve for induction of anesthesia. The **vertical axis** shows the percent of patients (on a probit scale) who did not open their eyes in response to the command. The **horizontal axis** represents doses of midazolam (on a log scale). Each **dot** represents a subgroup of five patients at the indicated dosage. A **horizontal** line at the ED_{50} level indicates the 95% confidence limits.

gle drug ED_{50} doses is presented in Table 2. In combination, the sum of the fractional doses was significantly lower than a single drug fractional dose (0.54 versus 1.0, $P < 0.0001$), indicating synergism. The ratio of a single drug fractional dose to a combined dose was 1.85. Thus, Table 2 indicates that approximately one-fourth of the single drug ED_{50} dose for each of the two agents would be needed in combination to induce anesthesia in 50% of the patients.

Discussion

The midazolam dose-response curve for induction of anesthesia (Fig. 1), which reflects the midazolam hypnotic effect, was very close to that reported early under similar conditions (13), both with regard to the position along the dose axis and the slope. As a result, midazolam ED_{50} values are very similar: 0.22 mg/kg (present study) and 0.19 mg/kg (13). Midazolam ED_{50} values reported elsewhere for the same end point also include 0.13 mg/kg (14) and 0.19 mg/kg (15) (cumulative doses). Wide differences in the induction doses of midazolam found by different authors are well known, and have been reviewed recently by Reves et al (6).

The alfentanil ED_{50} value of 0.134 mg/kg obtained in this study agrees with that reported elsewhere. In the study by McDonnell et al. (8), the ED_{50} value of alfentanil for loss of response to command was 0.092 mg/kg (unpremedicated patients, 10-s injection of the agent). At the same time, Silbert et al. (16) found that alfentanil, even in a dose of 0.200 mg/kg, did not induce anesthesia (response to the voice command) in five of ten unpremedicated patients. The difference is probably due to a slow (90 s) rate of the drug injection. With premedication (diazepam 10 mg orally), the injection of 0.120 mg/kg of alfentanil (over 10 s) induced anesthesia (response to command) in 13 of 19 patients (≈70%) (17).

The algebraic (fractional) analysis of drug interaction used in the present study demonstrated a synergistic midazolam-alfentanil interaction in relation to the hypnotic effect. Use of the ratio of single drug fractional dose to combined fractional dose provided the opportunity to measure the degree of alfentanil-midazolam hypnotic synergism ($r>1$), which reached an $r = 1.85$ level. Several investigators (1,2) have reported strengthening the hypnotic effect of benzodiazepines with opioid drugs in patients undergoing surgery. An increase of the percent of alfentanil-induced anesthetic induction by diazepam also was

Table 2. Alfentanil-Midazolam Interaction

	Equi-effective doses (ED_{50})					
	Alfentanil component		Midazolam component			
Groups	Fraction of ED_{50}	Dose (mg/kg)	Fraction of ED_{50}	Dose (mg/kg)	Sum of fractional doses	Ratio†
Alfentanil	1.00	0.13 (0.11, 0.19)	0.00	0.00	1.00	—
Midazolam	0.00	0.00	1.00	0.22 (0.15, 0.50)	1.00	—
Alfentanil and Midazolam	0.21	0.028 (0.018, 0.036)	0.33	0.07*	0.54 $P < 0.0001$	1.85

*Dose was kept constant (see Methods); †Ratio of single drug fractional dose to combined fractional dose.
P = significance of deviation from additivity.

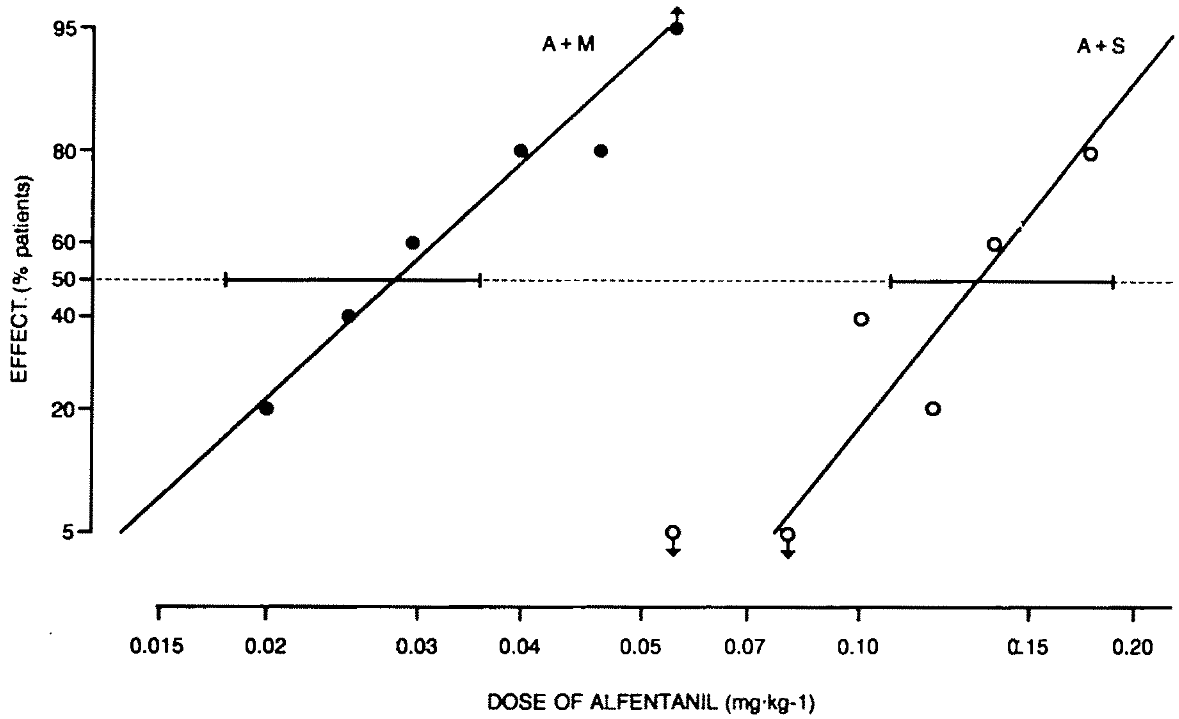


Figure 2. Alfentanil dose-response curves for induction of anesthesia with and without the addition of midazolam. A + M = dose-response curve for alfentanil with the addition of 0.07 mg/kg of midazolam (a constant dose that equals one-third of the midazolam ED_{50} value); A + S = dose response curve for alfentanil with the addition of isotonic saline solution instead of midazolam. Each **dot** represents a subgroup of five patients at the indicated dosage (**closed** for A + M, **open** for A + S).

found (16). Halliday et al. (18) have reported that pretreatment with alfentanil (0.3 mg/patient) increased the percent of patients who had anesthesia induced with midazolam (0.3 mg/kg) from 60 to 90%. Taking into account the very small dose of alfentanil, the effect of the combination suggests alfentanil-midazolam synergism.

The study by Stella et al. (5) demonstrated that naloxone (6 μg/kg intravenously) decreased the percent of patients rendered unconscious by diazepam 0.35 mg/kg (from 47 to 16%, $P < 0.001$) and, at the same time, did not change the hypnotic effect of thiopental. These results suggest that a nonspecific analeptic effect of naloxone did not influence the outcome of the study. Several experimental studies have suggested that opioid receptors are involved in producing some of the behavioral effects of benzodiazepines. For example, Billingsley and Kubena (19) reported that naloxone reversed the loss of the righting reflex induced by diazepam in mice without reversing the effects of either meprobamate or pentobarbital under similar conditions. In this and other studies (19–21) in rats, the anticonflict effect of diazepam was blocked by naloxone. Naloxone also blocked facilitation of lateral hypothalamic self-stimulation produced by chlordiazepoxide (22). Furthermore, diazepam induced rapid and pronounced changes in the enkephalin concentrations in specific areas of the brain in rats (23). This information indicates that opioid and benzodiazepine receptor systems may be complimentary in their hypnotic effect, which may explain the midazolam-alfentanil synergism demonstrated in our experiments.

Opioid-benzodiazepine combinations usually are used to achieve different components of anesthesia (24–26) with specific agents: a benzodiazepine for hypnosis and an opioid for blockade of the responses to noxious stimulation. We have shown that with the alfentanil-midazolam combination, the interaction of these two agents for hypnotic effect is synergistic.

We thank Roche Laboratories for providing support for this study.

References

1. Brown SS, Dundee JW. Clinical studies of induction agents XXV: diazepam. Br J Anaesth 1968;40:108–12.
2. Gamble JAS, Kawar P, Dundee JW, Moore J, Briggs LP. Evaluation of midazolam as an intravenous induction agent. Anaesthesia 1981;36:868–73.
3. Silbert BS, Rosow CE, Keegan CR, et al. The effect of diazepam on induction of anesthesia with alfentanil. Anesth Analg 1986; 65:71–7.
4. Lorens SA, Sainati SM. Naloxone blocks the excitatory effect of ethanol and chlordiazepoxide on lateral hypothalamic self-stimulation behavior. Life Sci 1978;23:1359–64.
5. Stella L, Crescenti A, Torri G. Effect of naloxone on the loss of consciousness induced by i.v. anaesthetic agents in man. Br J Anaesth 1984;56:369–73.
6. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology 1985;62:310–24.
7. Bovill JG. Which potent opioid? Important criteria for selection. Drugs 1987;33:520–30.
8. McDonnell TE, Bartkowski RR, Williams JJ. ED_{50} of alfentanil for induction of anesthesia in unpremedicated young adults. Anesthesiology 1984;60:136–40.
9. Forbes AR, Cohen NH, Eger EI II. Pancuronium reduces halothane requirement in man. Anesth Analg 1977;58:497–502.
10. Finney DJ. Probit analysis, 3rd ed. London: Cambridge University Press, 1971.
11. Berenbaum MC. Synergy, additivism and antagonism in immunosuppression. J Clin Exp Immunol 1977;28:1–18.
12. Ku HH. Notes on the use of propagation of error formulas. J Res Natl Bureau Stand 1966;70:263–73.
13. Tverskoy M, Fleysman G, Bradley EL Jr, Kissin I. Midazolam-thiopental anesthetic interaction in patients. Anesth Analg 1988;67:342–5.
14. Reves JG, Kissin I, Smith LR. The effective dose of midazolam. Anesthesiology 1981;55:82.
15. Gross JB, Caldwell CB, Edwards MW. Induction dose-response curves for midazolam and ketamine in premedicated ASA class III and IV patients. Anesth Analg 1985;64:795–800.
16. Silbert BS, Rosow CE, Keegan CR, Latta WB, Murphy AL, Moss J, Philbin DM. The effect of diazepam on induction of anesthesia with alfentanil. Anesth Analg 1986;65:71–7.
17. Palazzo MGA, Taylor S, Strunin L. Clinical experience with alfentanil for induction of anaesthesia; a comparison with thiopentone. Can Anaesth Soc J 1984;31:517–22.
18. Halliday NJ, Dundee JW, Harper KW. Influence of fentanyl and alfentanil pretreatment on the action of midazolam. Br J Anaesth 1985;57:351P–2P.
19. Billingsley LM, Kubena KR. The effects of naloxone and picrotoxin on the sedative and anticonflict effects of benzodiazepines. Life Sci 1978;22:897–906.
20. Soubrie PA, Jobert A, Thiebot MH. Differential effects of naloxone against the diazepam-induced release of behavior in rats in three aversive situations. Psychopharmacology 1980; 69:101–5.
21. Duka T, Cumin R, Haefely W, Herz A. Naloxone blocks the effect of diazepam and meprobamate on conflict behavior in rats. Pharmacol Biochem Behav 1981;15:115–7.
22. Lorens SA, Sainati SM. Naloxone blocks the excitatory effect of ethanol and chlordiazepoxide on lateral hypothalamic self-stimulation behavior. Life Sci 1978;23:1359–64.
23. Wuster M, Duka T, Herz A. Diazepam-induced release of opioid activity in the rat brain. Neurosci Lett 1980;16:335–7.
24. Woodbridge PD. Changing concepts concerning depth of anesthesia. Anesthesiology 1957;18:536–50.
25. Pinsker MC. Anesthesia: a pragmatic construct. Anesth Analg 1986;65:819–20.
26. Kissin I, Gelman S. Three components of anesthesia: one more reason to accept the concept. Anesth Analg 1987;66:97–8.

ANESTH ANALG
1989;69:218–25

Solubility of I-653, Sevoflurane, Isoflurane, and Halothane in Plastics and Rubber Composing a Conventional Anesthetic Circuit

Alexander G. Targ, MD, Nobuhiko Yasuda, MD, and Edmond I. Eger II, MD

TARG AG, YASUDA N, EGER EI, II. Solubility of I-653. Sevoflurane, isoflurane and halothane in plastics and rubber composing a conventional anesthetic circuit. Anesth Analg 198;69:218–25.

This study defines some characteristics of a standard anesthetic circuit that may impede anesthetic induction and recovery with I-653, sevoflurane, isoflurane, and halothane. Partition coefficients for anesthetic circuit components (masks, bellows, bags, airways, and circuit tubes) consistently ranked halothane > isoflurane > sevoflurane > I-653, suggesting a reverse order of washin and washout rates for an anesthetic circuit constructed from similar components. Consistent with this prediction, the concentrations of I-653 increased and decreased more rapidly than those of the other agents at any flow rate during washin (0.5, 1, or 2 L/min gas inflow rates) or washout (1, 3, or 5 L/min) in a conventional anesthetic circuit. The rates of change in I-653 concentration closely approximated the maximal possible theoretical rates.

Our results suggest that absorption of I-653 by circuit components or soda lime should not hinder induction of or recovery from anesthesia.

Key Words: ANESTHETICS, VOLATILE—halothane, I-653, isoflurane, sevoflurane. EQUIPMENT, ANESTHETIC CIRCUIT SYSTEM—closed, low flow. SOLUBILITY—partition coefficients.

I-653 is an inhaled anesthetic with a blood/gas partition coefficient of 0.42 (1), which indicates that it can produce rapid induction of and recovery from anesthesia. Rats anesthetized with I-653 recover more rapidly than those anesthetized with sevoflurane, isoflurane, or halothane (2).

Because I-653 is expensive to use, it likely would be applied in a low-flow or closed-circuit absorption system. Six factors govern the rate at which anesthesia can be induced with a low-flow system: the flow into the system; the volume of the system; the uptake of anesthetic by the patient; the concentration of anesthetic in the delivered gases; the extent to which circuit components absorb anesthetics; and the extent to which anesthetic is degraded by soda lime. Might absorption or degradation of I-653 by circuit components hinder the development of an anesthetizing concentration? To examine this question, we studied the solubility of I-653, isoflurane, halothane, and sevoflurane in plastics found in conventional anesthetic circuit components, and the impact of flow rate, absorption, and degradation on the increase and decrease of I-653 relative to other volatile anesthetics in a conventional anesthetic circuit.

Methods

First, we compared the solubility of I-653, sevoflurane, isoflurane, and halothane in anesthesia circuit components. In addition, we examined the washin and washout rates of these anesthetics delivered to a conventional anesthetic circuit system at various flow rates.

Solubility of Anesthetics in Circuit Components

We determined plastic/gas and rubber/gas partition coefficients of each circuit component with a modification of a method used previously (3). The density of a collection of thin pieces of each component was determined by adding a known mass of thin pieces of component to a 75-ml volumetric flask of known mass, filling the flask precisely to the 75-ml line with distilled water, and determining the combined mass.

Supported in part by the Anesthesia Research Foundation and in part by Anaquest.

Received from the Department of Anesthesia, University of California, San Francisco, CA 94143-0464. Accepted for publication February 28, 1989.

Address correspondence to Dr. Eger, Department of Anesthesia, University of California, Room S-455, San Francisco, CA 94143-0464.

©1989 by the International Anesthesia Research Society

For determination of solubility, known masses of thin pieces of each component [Vital Signs (Totawa, NJ) mask plate and pad, Marquest (Englewood, CO) corrugated circuit tube and Y-piece, Ohmeda (Madison, WI) ventilator bellows, Marquest (Englewood, CO) reservoir bag, Porges (Fairfield, NJ) nasal airway, and Mallinckrodt (Argyle, NY) endotracheal tube] were placed in separate flasks of known volume (about 575 ml). We assigned three flasks to each component, and sealed each flask with a Teflon stopper (pierced with a needle) that had a one-way stopcock (for sampling) coated at its upper portion with a small amount of Teflon grease. The flask was then evacuated to allow a known volume (50.05 ml) of a mixture of I-653 (1.09%), sevoflurane (0.42%), isoflurane (0.39%), and halothane (0.49%) to be drawn into the flask. The pressure within the flask was equilibrated with ambient pressure by briefly opening the stopcock.

Gas samples were withdrawn from the flask over 1- to 63-day intervals to determine the amount of time required for the circuit components to approximate equilibrium with the anesthetics. A state of equilibrium was assumed if there was no significant change ($P < 0.05$, Student's two-tailed, paired t-test) in any successive partition coefficients when the time allowed for equilibration was doubled. Using a 30-ml glass syringe attached to a nylon stopcock, we injected 15 ml of room air into each flask. The gas in the flask was barbotaged by withdrawing and reinjecting 15 ml 20 times, and the sample taken after the 20th injection. Each 15-ml sampling decreased the anesthetic concentration by approximately 3%, a decrease that we compensated for in our calculation of the partition coefficient.

Successive partition coefficients were calculated from the decreases in gas concentrations in samples taken from the flasks over a 9-week period. All samples were run in triplicate. The final partition coefficients were calculated from samples taken after 6–9 weeks.

Three control (dummy) flasks were prepared in a manner identical to the study flasks containing the circuit components. The gas concentrations in the dummy flasks were measured at the same sampling times as for the study flasks. With the passage of time, the concentration in the dummy flask decreased slightly because of the loss of anesthetic by leakage and absorption into the components of the flask (i.e., the Teflon stopper and grease). The decrease was more than could be accounted for by the dilution produced by sampling. The concentration in each experimental flask was corrected for loss as a result of leakage and absorption by assuming a decay rate identical to that in the dummy flasks.

Because disposable anesthetic circuits are exposed to anesthetics only for hours (rather than the period of days just described), we also determined the extent to which polyethylene circuit tubing and reservoir bags reach equilibrium with anesthetic gases during a 60-min exposure (i.e., we determined the "effective" partition coefficients). Circuit tubing and bags were chosen because, apart from soda lime, they provide the largest surface area for gas exchange in a typical circuit. Partition coefficient determinations of fresh reservoir bags and corrugated circuit tubes were repeated as before, except that we used a 10-fold lower concentration of anesthetic gases and a larger sample loop for injection into the gas chromatograph. The bags were cut into 4-cm-wide strips across their short axis, and the tubing was slit lengthwise along opposite sides and then cut across the short axis to create 4-cm-long half-cylinders. Samples were drawn at 7.5, 15, 30, and 60 min.

In at least one important respect, this test of the effective solubility did not mimic the clinical situation. In the flasks, anesthetic gas diffuses into the components from both inner and outer surfaces. In a circuit, the anesthetic vapor enters the components only from the inner surface. Assuming that both surfaces have identical diffusion characteristics, the decline in concentration of anesthetic vapor in the flask does not significantly decrease diffusion rates, anesthetic concentrations decline linearly with increasing distance penetrated into rubber and plastic, and diffusion into one surface does not slow diffusion into the opposing one (i.e., anesthetic has penetrated <50% of thickness from each side), we estimated that single-surface diffusion would achieve the same amount of anesthetic uptake in twice the time. Because anesthetic concentrations probably decline exponentially with increasing depth of penetration and because 50% penetration may be exceeded, this approach may underestimate the rate of equilibration. The progressive decrease in anesthetic concentration may have a similar effect.

All samples in the solubility, washin, and washout studies were analyzed for anesthetic concentrations by gas chromatography. We used a Gow Mac model 750 gas chromatograph equipped with a 30-m-long, fused silica, open tubular, capillary column (0.53-mm internal diameter) coated with a 5-μ-thick layer of methylsilicone oil [J&W Scientific (Folsom, CA) DB-1]. A nitrogen carrier stream of 6 ml/min was directed through the column, with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200°C was supplied by

Table 1. Plastic/Gas Partition Coefficients after 6 to 9 Weeks' Equilibration

Plastic components	I-653	Sevoflurane	Isoflurane	Halothane
Y-piece (polypropylene)	6.67 ± 0.03	7.68 ± 0.05	10.6 ± 0.3	19.1 ± 0.3
Mask plate (polycarbonate)	13.2 ± 2.3	12.4 ± 2.9	19.3 ± 4.2	25.7 ± 2.8
Circuit tube (polyethylene)	16.2 ± 1.3	31.2 ± 1.4	57.9 ± 1.3	128 ± 1
Reservoir bag (latex rubber)	19.3 ± 3.0	29.1 ± 3.4	48.9 ± 6.0	190 ± 5
Bellows (black rubber)	10.4 ± 1.0	22.6 ± 1.0	42.9 ± 5.8	199 ± 4
Nasal airway (latex rubber)	14.0 ± 0.7	28.1 ± 1.2	43.9 ± 10.9	215 ± 6
Endotracheal tube (polyvinylchloride)	34.7 ± 1.2	68.5 ± 1.3	114 ± 2	233 ± 2
Mask pad (polyvinylchloride)	51.7 ± 2.6	104 ± 3	170 ± 11	323 ± 3
Flask plug (Teflon)	19.4 ± 2.2	24.5 ± 2.6	33.8 ± 3.1	27.4 ± 2.6
Stopcock grease (Teflon)	31.8 ± 6.9	59.6 ± 7.1	89.9 ± 8.4	168 ± 8

Values are expressed as the mean ± SD.

hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop, except for the short-term equilibration samples, which were injected with a 0.5-ml gas sample loop. The chromatograph was calibrated with secondary tank standards that had been calibrated with primary standards produced by injection of a liquid aliquot of anesthetic into a flask of known volume.

Washin and Washout of Agents from an Anesthetic Circuit

The four anesthetics used in the studies of solubility were delivered to a standard anesthetic circuit at various flow rates to test the rate of washin and washout of each agent. The circuit was composed of three corrugated polyethylene tubes (Marquest), a polypropylene Y-piece and elbow (Marquest), a soda lime absorber including inspiratory and expiratory valves (Ohio Medical Products), fresh (15% water) soda lime (Dewey and Almy Sodasorb), a rubber bellows (Ohmeda) in a ventilator (Air-Shields Ventimeter ventilator), and a latex reservoir bag (Marquest) attached at the Y-piece elbow to simulate the patient's lungs. The total volume of the system, as measured by water filling, was 9860 ml.

We flushed the system with 100% oxygen at 3 L/min for 36 h before use and before adding soda lime. We also tested the system for leaks by observing a sustained volume in the system at flows ≤0.5 L/min during positive pressure ventilation. At these low flow rates, we detected no anesthetic (<0.1 ppm for all agents studied) before the start of anesthetic administration. The ventilator was set at a tidal volume of 500 ml, administered 25 times/min to circulate the gas in the system.

The flowmeter used to deliver anesthetic from a tank, which we had previously prepared, containing the four agents in 30% oxygen (balance nitrogen) was calibrated with a spirometer. An identical calibration was applied to the flowmeter used to deliver oxygen during the washout phase of the experiment. The flow rates for washin were 0.5, 1, and 2 L/min. Each washin continued for 60 min. The flow rates for washout were 1, 3, and 5 L/min. Each washout continued for 120 min. System samples were collected at 0.3, 1, 2, 3, 4, 5, 6, 8, 12, 20, 30, 40, 50, and 60 min during washin and at similar times plus 80, 100, and 120 min during washout. System samples were collected from the expiratory limb of the circuit, just distal to the expiratory valve. One test was done at each flow rate. During washin, inflow samples were collected at 4, 20, 40, and 60 min.

The delivered concentration (inflow samples) for each washin study was determined by averaging the four measurements made during that study. The system concentrations during washin were divided by the delivered concentrations to demonstrate graphically (washin curve) the approach to equilibration. The system concentrations during washout were divided by the concentration at the final sampling of washin (60 min) to demonstrate graphically (washout curve) the rate of anesthetic elimination from the circuit.

Results

In general, the order of the partition coefficients for the plastic and rubber components of the anesthetic circuit was halothane > isoflurane > sevoflurane > I-653 (Table 1, Figure 1). This relationship among partition coefficients was consistent at all times from 7.5 min to 9 weeks. These differences also held during the first hour of equilibration (in the two components tested) and at 6–9 weeks, except for the comparison of I-653 and sevoflurane for the mask plate. The latex reservoir bags equilibrated faster than the polyethylene tubing. Assuming one-surface diffusion, our results suggest the bags will be two to three times closer to equilibration than the tubing will

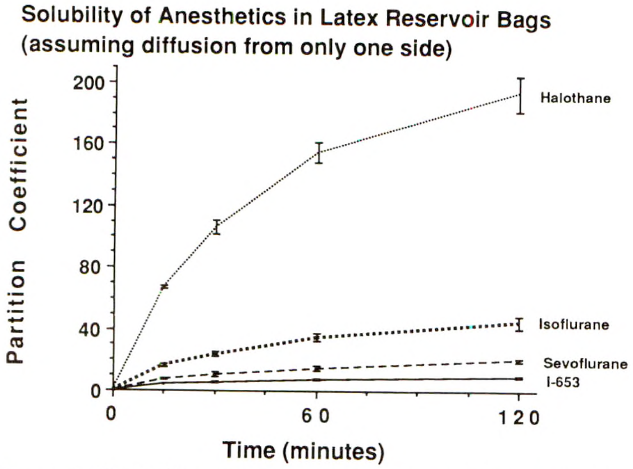


Figure 1. The "effective" rubber/gas partition coefficients for latex reservoir bags determined for times before equilibrium (the "effective" partition coefficient) increased with increasing duration of exposure and, in the course of an ordinary anesthetic, would be lower than the partition coefficients found at equilibrium. The ranking, however, is unchanged from that found with complete equilibration: halothane > isoflurane > sevoflurane > I-653. Each point is the mean of three determinations, with error bars displaying standard deviations.

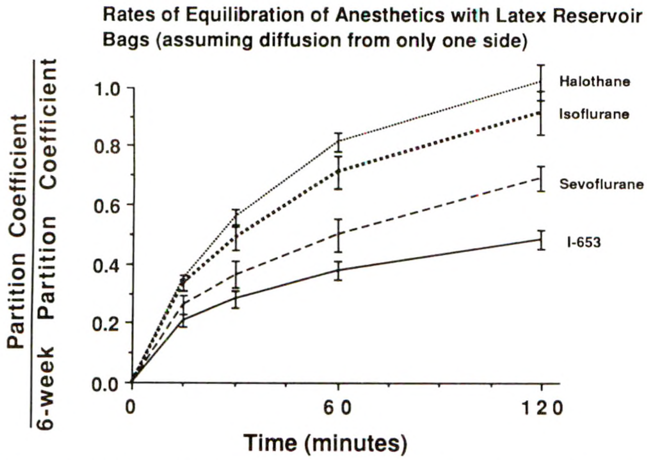


Figure 2. The rubber/gas partition coefficient for reservoir bags determined for times before equilibration (the "effective" partition coefficient) divided by the partition coefficient measured after 6 weeks is consistently lowest for I-653 over the period of an ordinary anesthetic. The order of the rates of equilibration is I-653 < sevoflurane < isoflurane < halothane. Data are from Table 1 and Figure 1. Each point is the mean of three determinations, with error bars displaying standard deviations (uncertainties in the 6-week value were ignored).

be after 2 hr of anesthetic exposure. In experiments with latex reservoir bags (Figure 1) and polyethylene circuit tubing (data not shown), the partition coefficients of I-653 were consistently lower than those of the other anesthetics. In the case of the latex reservoir bags, I-653 also consistently equilibrated more slowly than the other anesthetics (Figure 2). In the case of polyethylene tubing, however, we observed no consistent difference among anesthetic equilibration rates (data not shown).

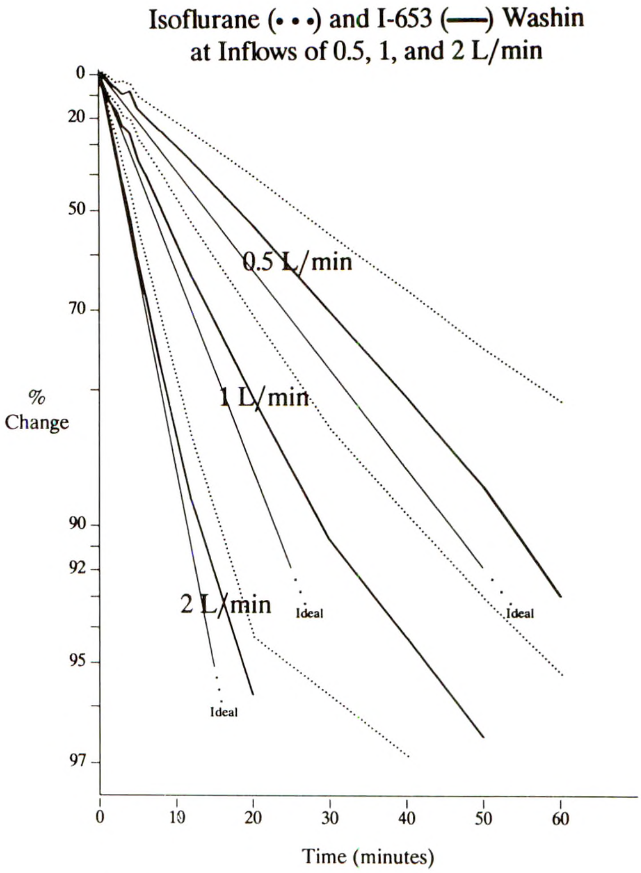


Figure 3. Washin rates for I-653 into a standard anesthetic circuit lie close to the ideal anesthetic rates of washin at inflows ($\dot{V}$) of 0.5, 1, and 2 L/min, deviating most from ideal at lower flow rates and near complete washin. The I-653 washin rate exceeded that of isoflurane at all inflows. Percent change was calculated from the equation: % change = 100 (inspired concentration)/(inflow concentration). Total volume of the system (Vs) was 9.86 L. Each graph represents the results of a single set of determinations. The lines labeled "ideal" are followed by ellipses and are given by the equation:

$$\% \text{ change} = 100[1 - e^{-(\dot{V}/Vs)t}],$$

where e = base of natural logarithms and t = time.

The rate of I-653 washin at all flows was greater than with isoflurane. The results for I-653 lay close to the line representing the behavior of a hypothetical ideal gas (i.e., one that is stable and insoluble in circuit components and mixes completely with the circuit gases as it enters the circuit) (Figure 3). As the circuit concentration approached the inflowing concentration, our ability to define accurately the difference between the two concentrations decreased (i.e., the "noise" in the two concentrations obscured the difference between the two concentrations). Consequently, percent changes greater than 97% are not presented.

Until percent change exceeded 70%, washin rates were I-653 > halothane > sevoflurane at all flows

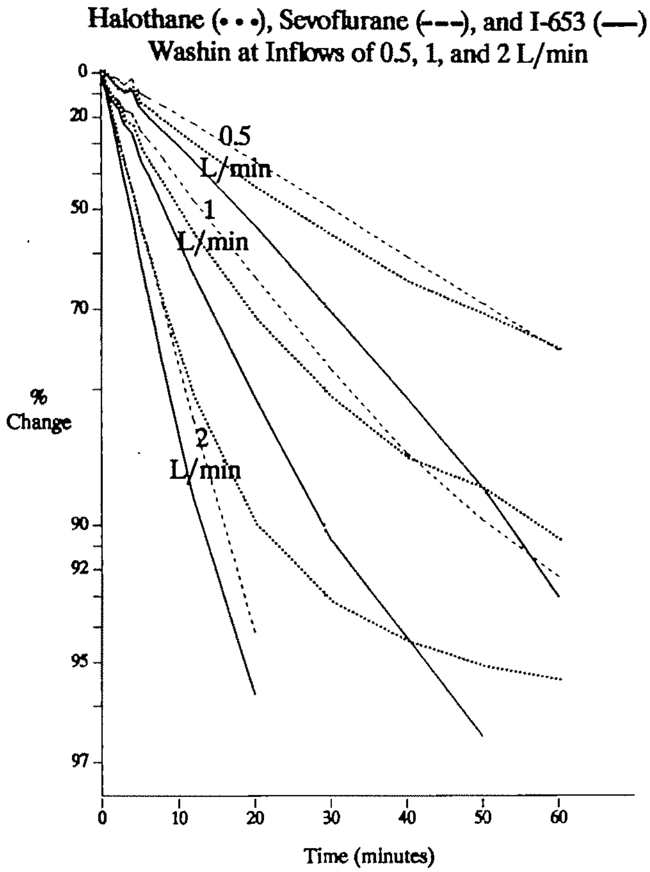


Figure 4. At any given inflow, the I-653 washin rate exceeded that of sevoflurane or halothane. Sevoflurane washed in more slowly than halothane or isoflurane until percent change surpassed 70%. During the final stages of washin, the sevoflurane washin rate eventually exceeded that of halothane at all flows and isoflurane at 2 L/min. Percent change was calculated from the equation: % change = 100 (inspired concentration)/(inflow concentration). Total volume of the system was 9.86 L. Each graph represents the results of a single set of determinations.

(Figure 4). Relative rates changed to I-653 > sevoflurane > halothane by 12 min for the 2 L/min flow, by 50 min for the 1 L/min flow, and by 60 min for the 0.5 L/min flow. Isoflurane washin was faster than halothane washin at all flow rates. Sevoflurane washin was slower than isoflurane washin at 0.5 and 1 L/min but more rapid at 2 L/min by 30 min.

The rate of washout of I-653 at all flows was greater than with isoflurane, with I-653 lying close to the line representing the rate at which an ideal anesthetic would washout (Figure 5). Previous workers (4) demonstrated washout rates faster than would be predicted for an ideal anesthetic based on their system's estimated volume (which was not precisely measured) and inflow rate. This discrepency may be explained by incomplete mixing, resulting from mechanical circulation insufficient for the inflow rate. We ensured adequate mixing by increasing mechanical gas circulation by a factor of 2 and decreasing

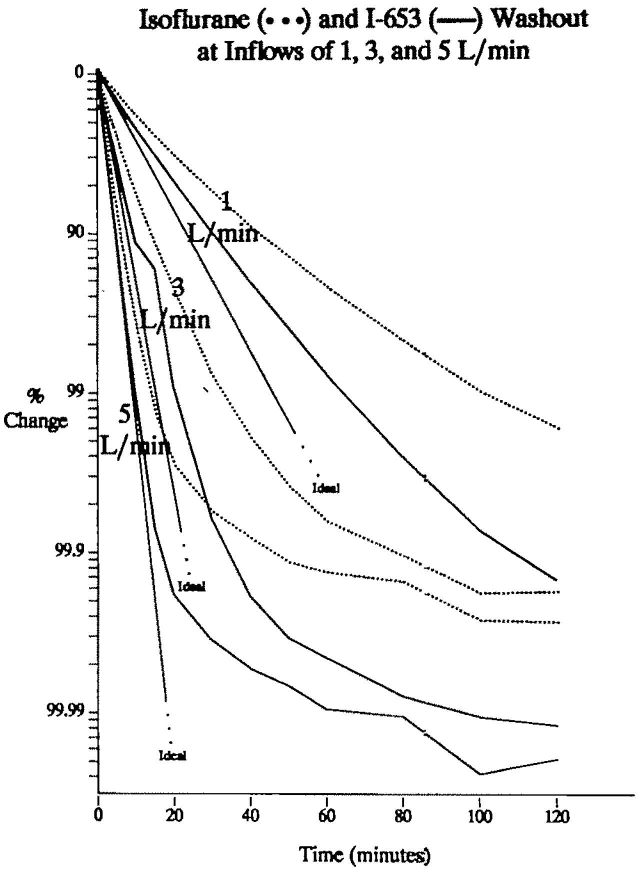


Figure 5. The washout rates of I-653 from a standard anesthetic circuit lie close to the ideal anesthetic rates of washout at inflows ($\dot{V}$) of 1, 3, and 5 L/min, deviating most from the ideal at lower flow rates and near complete washout. At any given inflow, the I-653 washout rate exceeded that of isoflurane. Percent change was calculated from the equation: % change = 100[1−(inspired concentration)/(initial concentration)]. Total volume of the system (Vs) was 9.86 L. Each graph represents the results of a single set of determinations. The lines labeled "ideal" are followed by ellipses and are given by the equation:

$$\% \text{ change} = 100[1 - e^{-(\dot{V}/V_s)t}],$$

where e = base of natural logarithms and t = time.

inflow by a factor of 2–20 as compared with those in the system in which this effect was reported. Until percent change exceeded 90%, washout rates were I-653 > halothane > sevoflurane at all flows (Figure 6). This ranking changed to I-653 > sevoflurane > halothane by 8 min for the 5 L/min flow, by 50 min for the 3 L/min flow, and by 80 min for the 1 L/min flow (Figure 6). Washout rates for isoflurane consistently exceeded those for halothane at all flow rates. Before 90% change, sevoflurane washed out more slowly than isoflurane. Sevoflurane had a slower rate of washout than isoflurane for 15 min at the 5 L/min flow, for 40 min at the 3 L/min flow, and for 80 min at the 1 L/min flow.

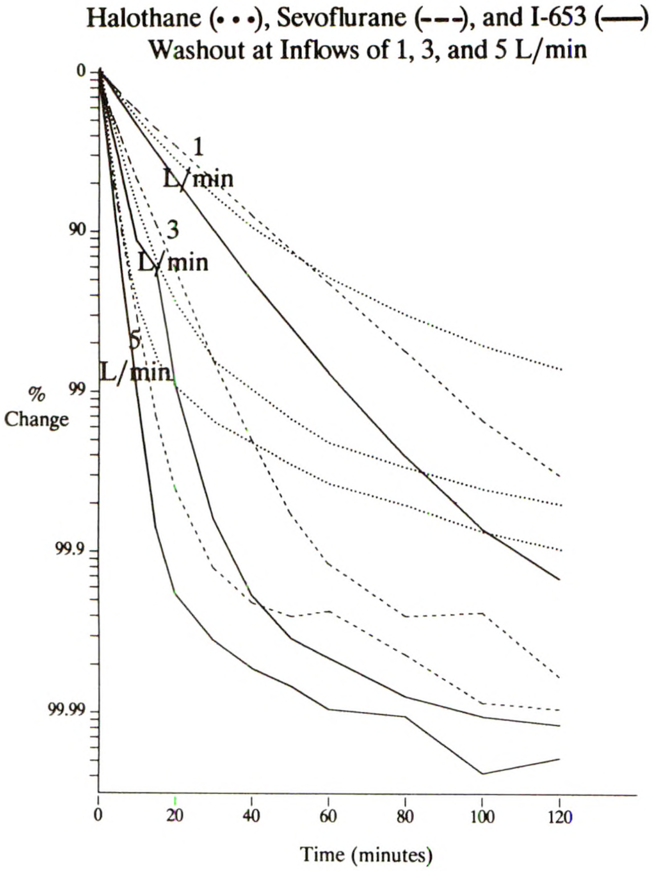


Figure 6. At any given inflow, the I-653 washout rate exceeded that of sevoflurane or halothane. Sevoflurane washed out more slowly than halothane and isoflurane until percent change exceeded 90%. During the final stages of washout, the washout rate of sevoflurane eventually exceeded that of isoflurane and halothane. Percent change was calculated from the equation: % change = 100[1−(inspired concentration)/(initial concentration)]. Total volume of the system was 9.86 L. Each graph represents the results of a single set of determinations.

Discussion

Our finding of a ranking of plastic/gas partition coefficients of halothane > isoflurane > sevoflurane > I-653 is consistent with results from previous studies of anesthetic solubility in plastic (3,5,6), tissues (1,5,7–11), and other solvents (1,7,8,12,13). Although our qualitative findings do not differ from previous results for halothane or isoflurane (results have not been described for sevoflurane or I-653), the quantitative results differ. We found larger plastic/gas partition coefficients than reported by previous investigators, probably because we allowed a longer time for equilibration. Even after allowing up to 147 days for equilibration, some of our samples failed to meet our definition of equilibrium. Previous studies have not recognized the need to allow for the small cumulative changes that occur over prolonged periods.

The slow approach to equilibrium that we observed has one other implication. The barrier to movement of anesthetic into and through plastics must be considerable. However, the barrier is not complete and, in the case of latex rubber, it may be overcome by halothane in 1–2 hr (Figure 2). This finding has an implication regarding contamination of operating room air with anesthetic vapors. Contamination by trans-rubber movement would be: halothane > isoflurane > sevoflurane > I-653. The magnitude of this source of contamination has been estimated based on studies of halothane diffusion through the walls of circuit tubing (14). The results suggest that in a well ventilated operating room equipped with a gas machine and ventilator, the amount of halothane contamination of operating room air attributable to diffusion through the circuit tubing walls is small compared with that from other sources.

Because absorption is not complete in the course of an ordinary anesthetic, the partition coefficients given in Table 1 overestimate the effective absorptive capacity of the circuit components. A better estimate is given by the data portrayed in Figure 1 for latex reservoir bags and by data described in the text for corrugated polyethylene tubing, the two major absorptive rubber and plastic components of an anesthetic circuit. However, even incomplete equilibration results in estimates of substantial absorption in the course of clinical anesthesia. It is this absorption that produces the hindrance to washin and washout portrayed in Figures 3–6. The approach to complete equilibration is more rapid with the latex reservoir bags than with the corrugated polyethylene tubing despite the similar wall thicknesses of 0.11 and 0.13 mm, respectively (i.e., latex rubber is more permeable to the anesthetic). This appears to be a function of the greater solubility of anesthetics in rubber. Similarly, we found that the rate of equilibration with components of low solubility (data not shown) was slower than the rate found with polyethylene.

The partition coefficients of Teflon flask plugs (19.4–27.4) and Teflon stopcock grease (31.8–168) demonstrated that these items have a substantial, previously unrecognized capacity to absorb anesthetic vapors. In our studies, we restricted the impact of absorption by these components on the calculated partition coefficients by minimizing the amount of Teflon grease and plastic exposed to the vapors and by making corrections obtained from the data from control flasks. In future studies, it might be advantageous to use materials composed of polypropylene or polycarbonate, which both have partition coefficients lower than that of Teflon. Not only were the partition coefficients associated with polypropylene and polycarbonate (and Teflon) low, but equilibration was also obtained slowly, giving still lower effective partition coefficients for short-term studies. Inorganic materials, such as glass and stainless steel, would create the least error.

Assuming first-order kinetics and anesthetic loss only by diffusion into circuit components and system venting, we expected and found greater deviation from the ideal rate of washin, and washout at lower than at higher flows. Thus, the low solubility and uptake of I-653 and sevoflurane are of considerable benefit to the clinical use of these agents because their high cost likely will dictate their use in low-flow systems. Conversely, the higher solubility of isoflurane and halothane is less of a problem because their lower cost permits the use of higher flow rates.

Because partition coefficients influence both the rate and amount of absorption of anesthetic (15), at a given rate of inflow, the ranking of the rates of washin and washout from the anesthetic circuit should be I-653 > sevoflurane > isoflurane > halothane. Although the I-653, isoflurane, and halothane curves followed in this order, sevoflurane washed in and washed out more slowly than both isoflurane and halothane, diverging from these predictions until washin and washout were almost completed. Soda lime binds and degrades sevoflurane far more than it does I-653, isoflurane, or halothane (16–18). Experiments conducted at 22°C suggest that for I-653, sevoflurane, isoflurane, and halothane, the soda lime/vapor "partition coefficient" increases with decreasing soda lime water content, approaching 0 for soda lime containing 10–15% water and, in the case of sevoflurane, reaching 42 for completely dried soda lime, a value at least threefold greater than that for any of the other anesthetics (Strum DP, personal communication). Thus, the slower than expected washin of sevoflurane may reflect reversible binding to soda lime combined with soda lime-mediated degradation. The slower washin and both slower and more rapid washout of sevoflurane compared with isoflurane are consistent with this hypothesis. During washin, less sevoflurane than isoflurane dissolved in circuit components other than soda lime, but soda lime both degraded and reversibly bound sufficient sevoflurane to retard its washin more than that of isoflurane. During early washout, release of sevoflurane bound to soda lime would slow sevoflurane washout, but during late washout, the soda lime degradation of sevoflurane may accelerate washout. Although the partition coefficients of anesthetic in soda lime are smaller than those for plastics and rubber, the large volume and surface area of soda lime make it a potentially capacious and rapidly exchanging reservoir.

The first 5 min of washout are most relevant to clinical practice because patients normally would be separated from the circuit after this time. At a 5-L/min flow rate, a flow typically used to initiate recovery from anesthesia, I-653 demonstrated a 91.7% decrease in concentration after 5 min of washout. Isoflurane, which had the second most rapid washout rate, did not decrease to this concentration until an additional 1 min had elapsed. With halothane and sevoflurane, this level was reached after an additional 8 and 13 min, respectively.

The rapid washout of I-653 means that anesthetic concentrations may be rapidly decreased to a low level with the use of high flows, and this decrease is substantially greater than that attained with other agents. As an example, after 2 hr of washout, the level of I-653 decreased ten times more than the level with isoflurane (Figure 5).

We thank Winifred von Ehrenberg for editorial assistance.

References

1. Eger EI II. Partition coefficients of I-653 in human blood, saline, and olive oil. Anesth Analg 1987;66:971–3.
2. Eger EI II, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: a test of the effect of anesthetic concentration and duration in rats. Anesth Analg 1987;66:977–82.
3. Eger EI II, Larson CP JR, Severinghaus JW. The solubility of halothane in rubber, soda lime and various plastics. Anesthesiology 1962;23:356–9.
4. Beebe JJ, Sessler DI. Preparation of anesthesia machines for patients susceptible to malignant hyperthermia. Anesthesiology 1988;69:395–400.
5. Vitcha JF. Table 2. Blood-gas partition coefficients. Table 3. Partition coefficients of Ethrane and Forane in rubber and plastic anesthetic circuit materials. Washington, DC: FDA, FDA New Drug Application for isoflurane 1975:2948.
6. Titel JH, Lowe HJ. Rubber-gas partition coefficients. Anesthesiology 1968;29:1215–6.
7. Strum DP, Eger EI II. Partition coefficients for sevoflurane in human blood, saline, and olive oil. Anesth Analg 1987;66: 654–6.
8. Larson CP JR, Eger EI II, Severinghaus JW. The solubility of halothane in blood and tissue homogenates. Anesthesiology 1962;23:349–55.
9. Eger EI II, Larson CP JR. Anaesthetic solubility in blood and tissues: values and significance. Brit J Anaesth 1964;36:140–9.
10. Yasuda N, Targ AG, Eger EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues (abstr). Anesthesiology 1988;69:A615.
11. Fiserova-Bergerova V. Gases and their solubility: a review of fundamentals. In Fiserova-Bergerova V, ed. Modeling of inhalational exposure to vapors: uptake, distribution, and elimination. Vol. I. Boca Raton, Florida: CRC Press, 1983:3–28.

12. Renzi F, Waud BE. Partition coefficients of volatile anesthetics in Krebs' solution. Anesthesiology 1977;47:62–3.
13. Koblin DD, Eger EI II, Johnson BH, et al. Minimum alveolar concentrations and oil/gas partition coefficients of four anesthetic isomers. Anesthesiology 1981;54:314–7.
14. Whitcher C, Piziali R, Sher R, Moffat RJ. Development and evaluation of methods for the elimination of waste anesthetic gases and vapors in hospitals (appendix B). Cincinatti: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Field Studies and Clinical Investigations; Washington, DC: U.S. Government Printing Office, 1975.
15. Leo A, Hansch C, Elkins D. Partition coefficients and their uses. Chem Rev 1971;71:525–616.
16. Eger EI II, Strum DP. The absorption and degradation of isoflurane and I-653 by dry soda lime at various temperatures. Anesth Analg 1987;66:1312–5.
17. Eger EI II. Stability of I-653 in soda lime. Anesth Analg 1987; 66:983–5.
18. Strum DP, Johnson BH, Eger EI II. Stability of sevoflurane in soda lime. Anesthesiology 1987;67:779–81.

ANESTH ANALG
1989;69:226–8

Ether Does Not Antagonize Bronchoconstriction Caused by Acetylcholine, Histamine, or Phenylephrine

Paul Neill, MB, ChB MRCP*, and James W. Sleigh, MB, ChB, FFARCS†

NEILL P, SLEIGH JW. Ether does not antagonize bronchoconstriction caused by acetylcholine, histamine, or phenylephrine. Anesth Analg 1989;69:226–8

The effect of ether as a possible antagonist of mediator-effected bronchoconstriction was tested in eight anesthetized, paralyzed, and mechanically ventilated baboons. Ether administered intravenously had no effect on bronchoconstriction caused by acetylcholine, histamine, or phenylephrine administered by the same route, either alone or in combination with propranolol.

Key Words: ANESTHETICS, VOLATILE—diethyl ether. LUNGS, BRONCHI.

Ether was frequently used in the past, and may still be of value in the management of severe attacks of acute asthma (1). The mechanism of action of ether in asthma, however, has not been extensively studied (2). Present opinion holds that ether anesthesia causes bronchodilation through adrenal catecholamine release, which in turn stimulates bronchial smooth muscle relaxation through β_2-adrenergic stimulation. Nonspecific direct smooth muscle relaxation may also play a part (3). Evidence is conflicting as to whether ether antagonizes cholinergic-, histaminic-, or α-adrenergic-induced bronchoconstriction (4–6).

The aim of the present study was to clarify the effect of ether on mediator-induced bronchoconstriction.

Methods

After obtaining institutional approval, eight unpremedicated baboons weighing between 10 and 16 kg were studied. Anesthesia was induced with intramuscular pentobarbital (30 mg/kg). This agent was used because it is considered to have little effect on bronchial tone (6).

After insertion of an intravenous cannula, the baboons were paralyzed with 1.25 mg of alcuronium intravenously, an oral endotracheal tube was passed, and the animals were ventilated with air using a sine wave ventilator (Palmer). The animals were kept in the supine position, with body temperature maintained at 37°C throughout the procedure. A tidal volume of 15 ml/kg at a frequency of 18 breaths/min was used. An esophageal balloon was placed at the level of the nipple line and adjusted to minimize cardiac and esophageal artifacts. Transpulmonary pressure (Ptp) was measured by a differential pressure transducer (CRI model 320) placed between the esophagus and the proximal end of the endotracheal tube. Airflow (V) was measured with a pneumotachograph (Godart). The pressure and flow signals were recorded graphically (Kipp and Zonen Multicorder BD 20). Total pulmonary resistance was calculated by dividing Ptp by the maximal flow rate. The elastic component was, therefore, included in the measurement.

Baseline Ptp and V were recorded, after which bronchoconstriction was induced with acetylcholine (2 mg), histamine (20 μg), and phenylephrine (200 μg) intravenously, each individually, allowing readings to return to the baseline value between each administration. On the basis of a pilot study, these doses were selected as sufficient to produce bronchoconstriction severe enough to probably represent maximal bronchoconstriction. Values for Ptp and V were recorded continuously throughout the experiment.

After administering the bronchoconstricting agents and allowing return to baseline values, each baboon received an anesthetic dose of ether given

---

Received from the Departments of *Clinical Pharmacology and †Anaesthetics, Godfrey Huggins School of Medicine, Avondale, Harare, Zimbabwe. Accepted for publication March 1, 1989.

Address correspondence to Dr. Neill, Department of Clinical Pharmacology, Godfrey Huggins School of Medicine, PO Box A 178, Avondale, Harare, Zimbabwe.

©1989 by the International Anesthesia Research Society

intravenously to remove the risk of explosion from the heated pneumotachograph head and to minimize irritant bronchoconstrictor reflexes resulting from inhaled ether. The anesthetic was administered as a 20% solution in 10% soya bean emulsion (Intralipid); the minimum alveolar anesthetic concentration (MAC) of ether in baboons was assumed to be similar to that in human patients. Using the closed circuit anesthesia model of Lowe and Ernst (7), a rate of infusion was calculated to give approximately 1:3 MAC for 13 min for a 10-kg animal. The technique involves a two-stage infusion with the induction dose of 15 ml intralipid (3 ml pure ether) given over 5 min, with the remaining 5 ml (1.2 ml ether) given over 8 min. In a preliminary study, this dose of ether was shown to anesthetize a baboon in the weight range of the animals in the present study for the approximate duration needed for the study.

Values for Ptp and V were recorded when the full amount of ether had been given. The infusion was maintained, and the same doses of acetylcholine, histamine, and phenylephrine were repeated, with Ptp and V being continuously recorded.

After a period to allow ether to be eliminated, each baboon was given 0.25 mg of propranolol intravenously, and the entire experiment was repeated. All animals recovered fully at the end of the experiment. Changes in airways resistance were analyzed for statistical significance using paired Student's *t*-tests.

Results

Ether alone had no bronchoactive effect compared with baseline values. The average percent change in total pulmonary resistance after receiving the various combinations of drugs is shown in Figure 1.

We were unable to demonstrate any effect of ether in diminishing bronchoconstriction caused by acetylcholine, histamine, or phenylephrine. In addition, there was no significant difference in the effect of ether on bronchoconstriction in the presence of propranolol as compared with that before the administration of propranolol.

Discussion

Previous studies of ether and bronchial contractility have reported conflicting results. Adriani and Rovenstine (6) studied changes in tracheal ring size measured under a light microscope. They found that a low concentration of ether caused mild dilation, whereas higher concentrations caused constriction. The addition of ergotamine, an α-adrenergic agonist, and eserine, a cholinesterase inhibitor, had no influence on the effect of ether.

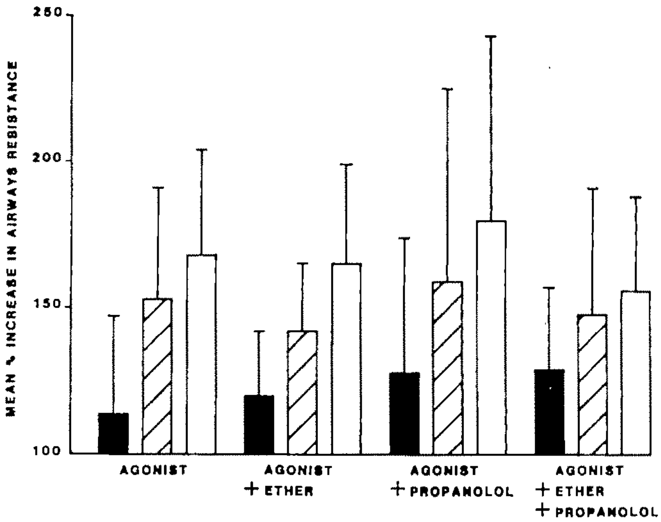


Figure 1. Histogram showing the mean percent increase (±SD) in pulmonary resistance caused by various combinations of drugs. ▨ = acetylcholine 2 mg; ☐ = histamine 20 μg; ■ = phenylephrine 0.2 mg.

Fletcher et al. (5) measured tension in chains of guinea pig tracheal rings. They found that ether caused relaxation of the smooth muscle and flattened the dose-response curve of the tracheal rings to acetylcholine. These effects, however, occurred at levels of ether considered to be lethal in guinea pig and humans.

The only in vivo study investigating ether was performed by Colgan (4), who measured dynamic compliance and airway resistance in spontaneously breathing dogs. In that study, there was no change from baseline measurements when ether was administered by inhalation in concentrations sufficient to cause the electroencephalogram to reach level four anesthesia. Some attenuation in bronchoconstriction caused by a high dose of histamine was, however, observed. Criticism of that study was directed at the possible effects of a change in respiratory rate (and thus airflow rates) and functional residual capacity in spontaneously breathing animals (2).

Previous studies, then, showed no pattern of change in tracheal or bronchial motor tone with ether alone, and possible interference with acetylcholine- and histamine-induced smooth muscle contraction.

Our study demonstrated no reduction in bronchomotor tone at rest when ether was administered. This is in agreement with the findings of Colgan (4) and other in vivo studies using other general anesthetics (5,8). This may reflect a very low in vivo bronchomotor tone in the majority of experimental animals. The relaxation of the tissues in the in vitro experiments may reflect increased tone before the administration of ether, possibly as a result of handling during the preparation of the equipment.

Our study was unable to detect any inhibition of the bronchoconstrictive effect of cholinergic, histaminergic, and α-adrenergic agonists. Although there was wide variation in response to the bronchoconstrictor agonists in the present study, each animal acted as its own control and thereby minimized interindividual variation. As such, we feel that our results are significant.

Ether has also been postulated to cause bronchodilation by means of endogenous catecholamine release. The administration of an adrenergic antagonist might be expected to block this effect. Propranolol alone did not cause bronchoconstriction and so, not surprisingly, it had no effect when administered with ether. After prior constriction with acetylcholine, histamine, and phenylephrine, there was similarly no change in the effect of ether after propranolol was added. It appears that catecholamine effects do not have an important role in the effect of ether.

Our study was designed to minimize the irritant bronchoconstrictor reflexes by administering all agents by the intravenous route. It is possible that ether reaches higher concentrations in bronchial smooth muscle when inhaled than when given intravenously. Therefore, a direct effect may account for the observed effect in asthma. Similarly, the intravenous dose may have been inadequate. However, as already mentioned, we were satisfied that this dose of ether produced surgical anesthesia of the expected duration. In preliminary studies, no bronchodilatory effect could be demonstrated using double or quadruple doses of ether. This was in marked contrast to the obvious complete attenuation of bronchoconstrictors when the animals were given intravenous atropine or phentolamine in clinically appropriate doses before the administration of acetylcholine or phenylephrine (unpublished data).

In conclusion, it would appear that despite clinical evidence of the efficacy of ether in the management of asthma, the mechanism of action by which ether produces bronchodilation remains unclear, but probably does not involve specific receptor interaction.

References

1. Robertson CE, Steedman D, Sinclair CJ, Brown D, Malcom-Smith N. Use of ether in life threatening acute severe asthma. Lancet 1985;1:187–8.
2. Aviado DM. Regulation of bronchomotor tone during anesthesia. Anesthesiology 1975;42:68–80.
3. Boissier JR, Gindicelli JF, Advenier C, et al. Sur le mechanisme de l'interaction ether-propanolol au niveau des bronches. Therapie 1970;25:523–38.
4. Colgan FJ. Performance of lungs and bronchi during inhalation anesthesia. Anesthesiology 1965;26:778–85.
5. Fletcher SW, Flache W, Alper MH. The actions of general anesthetic agents on tracheal smooth muscle. Anesthesiology 1968;29:517–22.
6. Adriani J, Rovenstine EA. The effect of anesthetic drugs upon bronchi and broncholes of excised lung tissue. Anesthesiology 1943;4:253–62.
7. Lowe HJ, Ernst EA. The quantitative practice of anesthesia; use of closed circuits. Baltimore: William and Wilkins, 1981:80.
8. Shah MV, Hirshman CA. Mode of action of halothane on histamine-induced airway obstruction in dogs with reactive airways. Anesthesiology 1986;65:170–4.

ANESTH ANALG 1989;69:229–38

Review Article

Noninvasive Transcutaneous Cardiac Pacing

Jeffrey S. Kelly, MD, and Roger L. Royster, MD

Key Words: HEART, RHYTHM—cardiac pacing. SURGERY, CARDIAC. TECHNIQUES, TRANSCUTANEOUS CARDIAC PACING.

Surgical patients often require temporary electrical pacing during their hospital course. Except for patients undergoing cardiac surgery, this pacing is usually accomplished by emergent transvenous pacemaker placement in the internal jugular, subclavian, femoral, or antecubital veins. Significant complications can arise from this procedure, particularly in hemodynamically unstable patients (1–3).

Recent technological advances have led to the rebirth of noninvasive transcutaneous cardiac pacing (NTP). NTP is safe, effective, easy to use, well tolerated by conscious patients, and produces hemodynamic responses similar to those produced by right ventricular (RV) endocardial pacing (4–7). It has proved efficacious for hemodynamically significant bradycardias (4) and now constitutes established second-line therapy after atropine for these arrhythmias (8). NTP may also be beneficial when used early during cardiopulmonary resuscitation (CPR) (4) or for overdrive pacing of tachyarrhythmias (9). Efficacy during general anesthesia (10) as well as perioperatively in cardiac surgery (11) has been well documented. Based on these facts, NTP is rapidly becoming the treatment of choice in clinical situations requiring emergency cardiac pacing. We review the history, pertinent electrophysiology and hemodynamics, and clinical uses of NTP, particularly in relation to the use of NTP in the perioperative period.

Historical Perspectives

Zoll (12) first reported the use of NTP in 1952, describing two successful resuscitations from ventricular standstill utilizing subcutaneous chest needle electrodes and low voltage monophasic DC current delivered over 2 ms. He went on to develop the first transcutaneous cardiac pacemaker consisting of an external DC pulse generator, 2-ms pulse duration, and 3-cm diameter metal paddles. Multiple successful resuscitations from Stokes-Adams attacks and ventricular standstill were subsequently reported with use of this technique (13–16). NTP, therefore, was the first widely accepted method of cardiac pacing. Discomfort, however, from cutaneous nerve stimulation, pectoralis muscle contraction, and local soft tissue damage proved intolerable to many conscious patients. In addition, rhythm recognition was obscured by the large pacing artifact, and pulses were difficult to palpate because of vigorous muscle contractions. With the development of transvenous pacing techniques in the early 1960s, NTP rapidly fell into disfavor.

A dramatic resurgence of interest in NTP has been influenced by two major factors: the inadequacies of transvenous pacing during CPR and technological improvements in NTP. Transvenous pacemakers have limited utility in the setting of cardiac arrest, asystole, and CPR because the technique is time-consuming, requires more technical skill, and has a high complication rate with emergent use, even in skilled hands (1–3). Balloon-tipped, flow-directed pacing electrodes, in addition, tend to work poorly in hypotensive patients. Most importantly, transvenous pacing does not improve outcome after cardiac arrest (17,18). Technological advances over the last 30 years include: 1) large surface area electrodes for stimulus transmission; 2) low density, constant-current impulses; 3) high impedance, gelled conductive medium; and 4) pulse durations of up to 50 ms. As a

---

Received from the Department of Anesthesia, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina. Accepted for publication February 14, 1989.

Address correspondence to Dr. Kelly, Department of Anesthesia, Bowman Gray School of Medicine, Wake Forest University, 300 South Hawthorne Road, Winston-Salem, North Carolina 27103.

©1989 by the International Anesthesia Research Society

result of these developments, cutaneous nerve stimulation has been virtually eliminated and skeletal muscle contraction markedly diminished (19). Myocardial thresholds actually decrease under these conditions (20). A comparison of the strength-duration curves of skeletal and cardiac muscle explains this apparent discrepancy. Skeletal muscle is maximally activated by high intensity stimuli of short duration (<1 ms), whereas thresholds for cardiac muscle stimulation continue to decrease with pulse durations up to 40–50 ms. Thus, judicious chest electrode placement over areas of minimal muscle mass can achieve effective cardiac stimulation with little or no skeletal muscle activation. These same stimulation characteristics have minimized cutaneous nerve stimulation (previously intolerable over 15 ma with older models) by maintaining the current delivered per unit time per cm^2 skin below cutaneous nerve threshold. Internal filtering has so reduced the stimulus and skeletal muscle artifact as to allow oscilloscope monitoring and recording. More recent models also incorporate mechanisms to sense depolarization or repolarization forces, thus permitting use in the demand (VVI) mode as well as asynchronously (VOO). Finally, advances in microcircuitry have also led to increased portability with currently available models weighing as little as 2.7 kg.

Various NTP models are currently marketed in the United States, some of which also include defibrillation units (Figure 1). Prices, sizes, and capabilities vary (Table 1). Models lacking sweep oscilloscope and/or defibrillator functions are compatible with commercially available units. Although it has been suggested that marked differences exist among competing NTP models with respect to patient comfort, ability to achieve electrical capture, and mean thresholds (21), no well controlled trials comparing the different devices have been published.

Electrophysiology

Further study has led to a more complete understanding of the pertinent electrophysiology of NTP. Initial work in dogs by Vargese et al. (20) demonstrated a significant diminution in NTP threshold with pulse durations up to 50 ms (74 ma) compared with 2 ms (138 ma). Atrial and ventricular activation were found to be simultaneous (20). The latter finding has since been contested in human volunteers, whose esophageal electrocardiograms (ECG) demonstrate ventricular activation with retrograde atrial conduction (22,23). Two recent investigations involving patients undergoing cardiac catheterization have clearly confirmed right ventricular activation both electrophysiologically and hemodynamically. One study, using intracardiac ECG, demonstrated an RV apex—His bundle—RV basal septum activation sequence (9), whereas another recorded simultaneous right and left heart hemodynamics and documented that the RV pressure curve upstroke preceded that of the left ventricle (24). Additional animal work has shown that the "pacing window" requiring the lowest threshold for capture with use of 10 ms pulse durations corresponds to the region of the apical impulse, with optimal electrode size appearing to be 5 cm^2 in diameter (25). Falk and Ngai (26) confirmed this result in humans, concluding that exact electrode placement is not crucial as long as the anterior (apical) electrode is negative. Polarity reversal in this study (that is, negative electrode posteriorly, positive electrode anteriorly) resulted in only 1 of 10 healthy volunteers being successfully paced. Geddes et al. (27) studied 50 human subjects, constructing strength-duration curves for pacing and for pain. Their conclusions suggest that the optimal stimulus duration for pacing with minimal pain is 10 ms (27). Thus, a 20–40-ms pulse duration delivered anterior to posterior across the heart affords maximal patient comfort while minimizing myocardial thresholds and skeletal muscle stimulation. Typical electrode position for maximal efficacy involves centering the anterior electrode along the left costal margin just to the left of the xiphoid process (thus avoiding the bulk of the pectoralis major muscle), with posterior electrode placement at the inferior aspect of the left scapula between the scapula and the thoracic spinous processes (Figure 2).

Hemodynamics

Hemodynamically, NTP appears to be at least equivalent to RV endocardial pacing. While preliminary data in normal animals had suggested this result (20), further research has lent supporting evidence. Niemann and associates (28) initially compared NTP with RV endocardial pacing and tongue-to-epigastrium pacing in a closed-chest, chronic heart block canine model. Compared with control and RV endocardial pacing, NTP at similar heart rates resulted in improved mean arterial pressure and cardiac output, in part due to decreases in systemic vascular resistance, whereas arterial or mixed venous blood gas samples were unaffected (28). A more recent comparison by Syverud et al. (5) using a similar model demonstrated comparable, stable hemodynamics during the 60-minute study period.

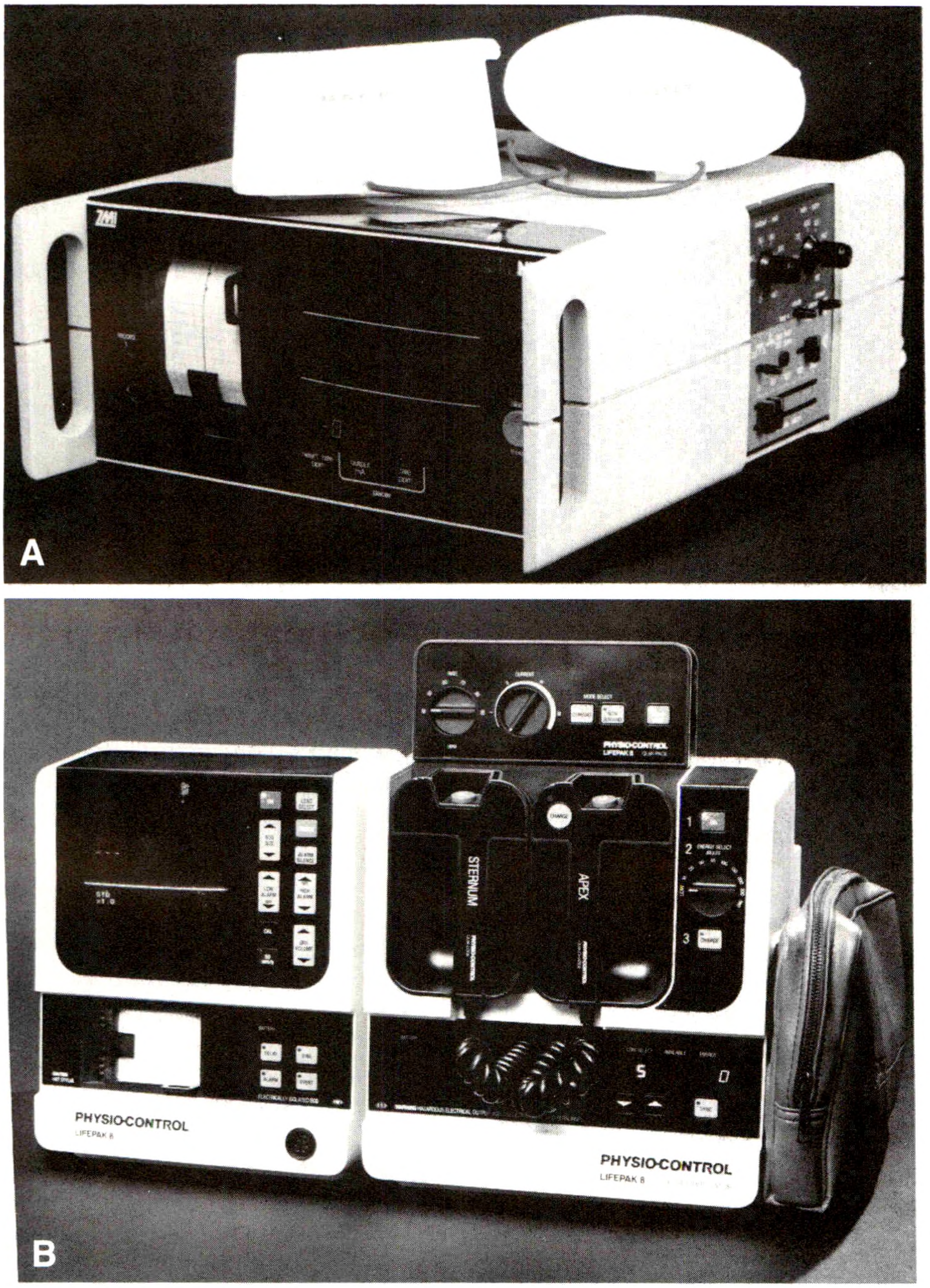


Figure 1. Examples of commercially available NTP units. **A,** Zoll NTP (ZMI Corporation, Cambridge, MA). **B,** LIFEPAK-8 (Physio-Control Corporation, Redmond, WA).

Two-dimensional and M-mode echocardiography in healthy human volunteers has documented uniform left ventricular contraction and unchanged fractional shortening with NTP compared with baseline sinus rhythm findings. No change in the movement of the interventricular septum was demonstrated, implying near-simultaneous contraction of both ventricles (29). This result is in contradistinction to RV endocardial pacing, where abnormal septal motion similar to left bundle-branch block (LBBB) is typically noted. Blood pressure in this study did not change despite the loss of coordinated atrial systole.

Although multiple clinical studies have reported equal increases in blood pressure when NTP and RV endocardial pacing are used sequentially (4,6), the first definitive hemodynamic data in humans were recently published by Feldman and associates (24). They studied NTP in 16 cardiac catheterization patients with simultaneous right and left heart hemodynamic recording. After obtaining baseline measurements, NTP was applied at 90 beats/minute and gradually increased to 85% of age-predicted maximal heart rate for 5 minutes or until angina was precipitated. A second set of data was then collected fol-

Table 1. NTP Model Comparisons

Manufacturer	Model	Pacing Modes	Built-in Oscilloscope/ Strip Recorder	Built-in Defibrillator	Pulse Duration (ms)	Rate Range (beats/min)	Milliamps (range)	Refractory Period (ms)	Approximate Battery Life (hr)	Weight (lb)
Laerdal Manufacturing Corporation	PaceAid 53	VOO/VVI	No/No	No	20	50/160	10–150	300	6	6
Physio-Control Corporation	Quik-Pace	VOO (VVI when used with cardiac monitor)	No/No	No	20	40/170	0–200	200–340 (rate-dependent)	2	9
	LifePak 8	VOO/VVI	Yes/Yes	Yes	20	40/90	0–200	340	1	38
ZMI Corporation	NTP 1000	VOO/VVI	Yes/Yes	No	40	30/180	0–140	100	2	18
	PD 1200	VOO/VVI	Yes/Yes	Yes	40	30/180	0–140	100	2	27

VOO = fixed rate; VVI = demand.

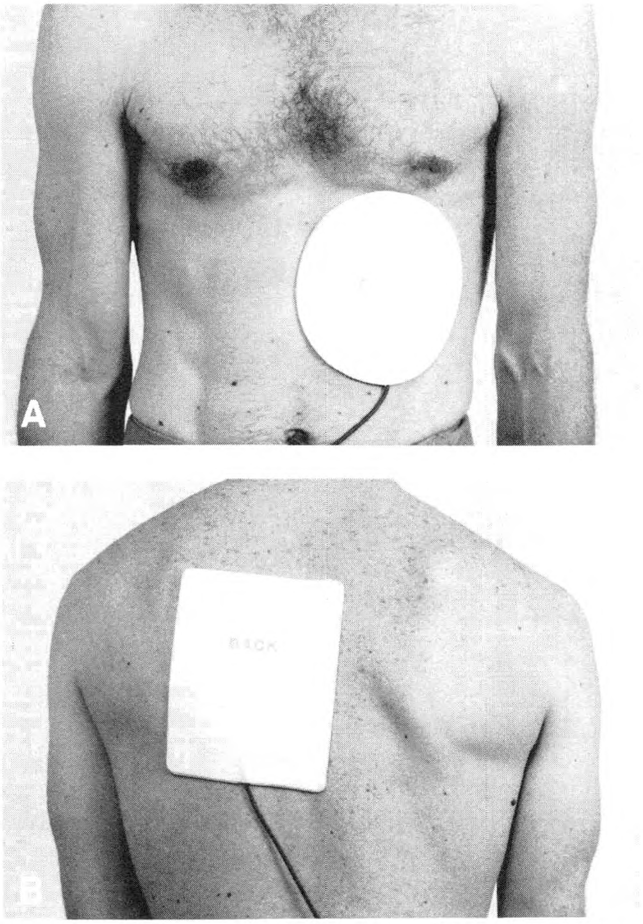


Figure 2. Recommended NTP electrode position for proper use. **A,** Anterior Electrode. **B,** Posterior Electrode.

lowed by abrupt termination of NTP, with final measurements obtained immediately after termination of NTP. At maximal pacing, all 16 patients demonstrated increases in right atrial, pulmonary artery, and mean aortic pressures. Increased O_2 consumption during NTP was compensated for by an increased arteriovenous O_2 difference, allowing cardiac index to remain unchanged. After NTP, however, cardiac index increased significantly, causing normalization of the arteriovenous O_2 difference. Systemic vascular resistance remained unchanged. Angina was precipitated in 8 of 16 patients, all of whom developed significant elevations of left ventricular end-diastolic pressure consistent with post-NTP ischemia. This response was not seen in the eight asymptomatic patients. Thirteen patients were subsequently shown to have significant coronary artery disease, including all eight patients who experienced angina. Additional human data have been published by Trigano et al. (30), who demonstrated a significant decrease in left ventricular systolic pressure with NTP compared with sinus rhythm and AV sequential pacing, but no change compared with VVI pacing. However, systolic index increased significantly with NTP compared with VVI pacing, inferring some beneficial effect related to chest wall stimulation. This occurrence may in part explain the case reported by Murdock et al. (31) describing NTP-induced CPR. Their patient could not maintain an adequate blood pressure (63/41 mm Hg) and cardiac output (3.6 L/min) with RV endocardial pacing, but NTP at a similar rate caused marked chest and abdominal muscle stimulation as well as vastly improved hemodynamics (48% increase in mean arterial pressure, 19% increase in cardiac output). These findings were reproduced when RV endocardial pacing was delivered with simultaneous abdominal compressions, leading the authors to speculate that mechanisms similar to "cough CPR" may be involved. Caution must be used, as with any ventricular pacing technique, in patients with reduced ventricular compliance. Dependence on atrial systole for adequate ventricular filling predisposes such patients to hemodynamic instability during any type of ventricular pacing.

Safety

The excellent safety record of NTP is attested to by the absence of long-term complications or deaths in either animal or human studies. The initial work by Zoll et al. (32) in dogs with normal sinus rhythm, complete heart block, and anoxia sufficient to produce multiple cardiac arrhythmias demonstrated that provocation of repetitive ventricular responses, ventricular tachycardia, and ventricular fibrillation (VF) required greater than 10 times the pacing threshold, a current exceeding the output of commercially available devices. More recent animal work (33) has confirmed this observation, showing that a stimulus of any given duration between 1 and 50 ms required at least 12 times the current necessary for pacing to produce VF. In an important histopathologic study, Syverud and colleagues (34) studied asynchronous use for 30 minutes in healthy dogs. No repetitive or sustained ventricular arrhythmias occurred in spite of multiple documented R-on-T phenomena. Serial ECGs and cardiac isoenzyme levels were normal with no animal developing clinical signs of cardiac dysfunction. Sacrifice and pathologic examination at 72 hr revealed minimal, insignificant cardiac lesions with no abnormalities of skin, skeletal muscle, or lungs (34). A similar study (29) in healthy human volunteers has documented no significant changes in serum levels of myoglobin, total creatinine phosphokinase, creatinine phosphokinase MB fraction, or lactate dehydrogenase. Falk et al. (6) subsequently described NTP to be safe, effective, and well-tolerated in humans. Thresholds averaged around 55 ma, with higher thresholds being necessary for patients with hemodynamically significant bradycardias (78 ma). No arrhythmias were noted.

Although subsequent resuscitation studies (35) have reported ventricular arrhythmias on rare occasions, larger clinical trials have not borne this out even in populations at high risk (4,24). The only reported case directly implicating NTP in inducing arrhythmias involved a 3-year-old boy with endocarditis and aortic root abscesses. Sudden development of complete heart block and cardiovascular collapse prompted a trial of NTP. Three consecutive NTP attempts resulted in ventricular tachycardia due to vulnerable period stimulation, with immediate reversion to complete heart block on cessation of NTP. Emergency thoracotomy subsequently revealed rupture of the aortic root into the pericardium and left pleural space; the patient died intraoperatively (36).

Local skin irritation and erythema can develop under the pacing electrodes in a small number of patients, but to our knowledge, no one has reported significant skin injury related to NTP use in humans. Similarly, no reports of electrical shock to patients or medical personnel appear in the literature, even when NTP is used concomitantly with CPR outside the hospital, that is, pre-hospital or in the emergency department (see clinical studies section).

Clinical Studies

Clinical enthusiasm for NTP has been generated mainly by those interested in bradyasystolic cardiac arrest and CPR. Although many case reports describe successful resuscitation utilizing NTP (37–42), most of these involve patients not yet in full cardiac arrest. Larger, more controlled clinical series have invariably yielded disappointing results (Table 2). Extensive pre-hospital trials have documented few long-term survivors regardless of whether NTP was used before, during, or after standard advanced cardiac life support (ACLS) interventions (43–47). When compared with ACLS in this setting, no appreciable improvement in resuscitation rates or outcome can be demonstrated (48,49). Similar results were shown with initial emergency department use of NTP (35,50–52), as well as its use for in-hospital cardiac arrests (53–55). Of note in most of these studies was the significant period of established cardiac arrest before NTP use (often greater than 15–20 minutes). The study by Clinton et al. (52) of 37 critical emergency department patients typified this early experience. Eight of their patients were successfully paced with six ultimately being discharged from the hospital. Five of these six survivors had presented in complete heart block or with hemodynamically significant bradycardia. The other survivor had a brief episode of asystole. Of the 29 patients who did not respond to pacing and received only ACLS, 5 survived to discharge.

More recent investigations, however, suggest that NTP may have a beneficial effect if used early enough after cardiac arrest. Barthell et al. (49) randomized 239 pre-hospital arrest victims on alternate days into ACLS only or ACLS plus NTP. Improved resuscitation rates were shown in patients paced earliest, with all surviving paced patients receiving NTP within 17 minutes or less. However, no significant differences were found between overall resuscitation rates (20.6% versus 21.4%, respectively) or survival (6.8% versus 4.4%, respectively). No patients in either

Table 2. Summary of NTP Use During Bradyasystolic Cardiac Arrest

Authors	Setting	No. of Patients Undergoing NTP	No. with Successful NTP ECG Capture	No. with Palpable Pulses	No. Surviving to Discharge
1) Paris et al.[43]	Pre-hospital	112	55/105 (52%)	9/112 (8%)	0/112 (0%)
2) Falk et al.[44]		20	8/20 (40%)	2/20 (10%)	1/20 (5%)
3) Eitel et al.[45]		91	85/91 (93%)	10/91 (11%)	0/91 (0%)
4) Feldman et al.[46]		6	3/6 (50%)	3/6 (50%)	0/6 (0%)
5) Barthell et al.[49]		103	Not stated	22/103 (21%)	7/103 (6.8%)
6) Hedges et al.[48]		101	Not stated	20/101 (20%)	6/101 (6%)
7) Dalsey et al.[35]		52	26/52 (50%)	8/52 (15%)	0/52 (0%)
8) Jaggarao et al.[47]		24	Not stated	2/24 (8%)	1/24 (4%)
9) White et al.[50]	Emergency Department	20	2/20 (10%)	0/20 (0%)	0/20 (0%)
10) Olson et al.[51]		12	4/12 (33%)	1/12 (8%)	0/12 (0%)
11) Clinton et al.[52]		37	Not stated	8/37 (22%)	6/37 (16%)
12) Syverud et al.[57]		19	14/19 (74%)	9/19 (47%)	2/19 (10%)
13) Knowlton et al.[53]	Emergency Department/ In-patients	26	12/26 (46%)	2/26 (8%)	0/26 (0%)
14) Noe et al.[54]		24	Data inadequate	3/24 (12.5%)	Not stated
15) Jansen et al.[55]	Intensive Care Unit	19	Not stated	3/19 (16%)	Not stated

group survived when palpable pulses were absent after 20 minutes of resuscitative efforts. NTP's effectiveness in the emergency stabilization of bradycardia and/or asystole during acute myocardial infarction was similarly documented by Worley and Bride (56). All 18 patients in their study demonstrated electrical capture with 13 being successfully resuscitated. A major limitation of this investigation was that no outcome parameters were reported. In probably the best clinical trial to date, Zoll and colleagues (4) studied 134 patients in a multi-center effort. Four patient categories were defined: 1) an emergency arrest group (60 patients); 2) an expected arrest group in which the likelihood existed of imminent asystole, bradycardia, or tachycardia (26 patients); 3) a standby group in which NTP was tested and kept in emergency readiness, but never needed in treatment (40 patients); and 4) tachycardia group in which stimulation was applied to terminate or provoke tachyarrhythmias. The two arrest categories were then subdivided into "brief" (less than 5 minutes) and "prolonged" (greater than 5 minutes). Of the 86 subjects constituting both arrest categories, 43 were successfully resuscitated with use of NTP (35 "brief" arrest victims compared with 8 "prolonged" individuals). Thirty-four of the 40 "brief" patients survived to discharge as opposed to only 4 of 46 "prolonged" patients. A smaller, more recent study by Syverud et al. (57) supports this data, demonstrating that two of five victims who underwent NTP within 5 minutes of cardiac arrest sustained full neurologic recovery. The 14 remaining patients had NTP applied between 5 and 20 minutes from the onset of resuscitation, and none regained complete neurologic function (57). Thirty-four of the 40 patients in Zoll's standby category avoided transvenous endocardial electrode placement for periods up to 1 month, and only 24 of the total patient population of 134 ultimately required this modality.

However, Knowlton and Falk's study (53) of in-hospital cardiac arrests did not support these more optimistic findings. NTP was used in 26 of 58 cardiac arrests, with approximately 75% of the pacing efforts initiated within 5 minutes from the onset of cardiorespiratory collapse. Although 12 of these 26 patients demonstrated electrical capture, only 2 had palpable pulses related to NTP and neither survived. Of the remaining 32 arrests in which NTP was not utilized (that is, those receiving only standard ACLS), 17 (53%) were successfully resuscitated. However, 13 of the 23 bradyasystolic events in the non-paced group rapidly responded to ventilatory support and medications, whereas NTP was initiated only in those patients who did not respond to initial ACLS interventions. Whereas their overall survival rate was 34%, it was only 6% (1/17) with either therapy when bradyasystolic arrest occurred due to severe metabolic derangements.

A second major clinical application of NTP involves its use for overdrive suppression of tachyarrhythmias. Although multiple case reports attest to NTP's effectiveness in ablating supraventricular (58,59) and ventricular (58–62) tachycardias as well as runaway pacemaker rhythms (63), only recently have Luck et al. (9) confirmed the efficacy of NTP burst suppression pacing. They compared conventional RV endocardial burst suppression pacing with NTP burst suppression, modifying their NTP unit to allow for tracking of stimuli from a standard programmable stimulator. In addition, the upper rate limit of their NTP was increased by reducing the refractory period of the device. They subsequently studied 14 patients electrophysiologically, inducing ventricular tachycardia by programmed right ventricular extrastimulation. Sixteen episodes of hemodynamically stable ventricular tachycardia reproducibly terminated by endocardial burst pacing were then subjected to NTP burst pacing. Fourteen of the sixteen episodes (88%) were ablated with NTP, requiring from 5 to 20 NTP captures for termination. NTP baseline thresholds were significantly lower than NTP burst suppression thresholds (76 ma versus 107 ma, respectively).

Many other clinical uses of NTP have been reported. These include: 1) antiarrhythmic drug toxicity (4,29,64); 2) post-countershock (4) and post-cardioversion (4,65) bradyarrhythmias; 3) hyperkalemia (4,29,52); 4) permanent pacemaker failure, infection, or during generator replacement (4,40); 5) cardiac catheterization and angiography (4,24,42); 6) acutely (41,56) and prophylactically (4,56) in the setting of acute myocardial infarction; 7) treatment of accentuated vagal states (4,66); and 8) prophylactic use during pulmonary artery catheterization in patients with left bundle-branch block (67). NTP has also been successfully adapted to infants and children with threshold and safety results similar to those of adults (68).

NTP and Anesthesia

Because many of the described situations can arise in the operating room, NTP may benefit surgical patients as well. Interestingly, there has been little evaluation of NTP under anesthetic conditions. Although eight patients in the multicenter study of Zoll et al. (4) were receiving anesthesia, no specific details of any of these procedures were reported. The study by Berliner et al. (10) comprises the first completed evaluation of NTP in adults in the operative setting. Twenty-one male patients undergoing elective general anesthesia were studied with use of an older NTP model generating 10–20 ms pulse durations. Although all patients demonstrated successful capture, half required the maximal unit output (200 ma). Neither evidence of organic heart disease, as indicated by history and/or preoperative ECG, nor total body surface area were predictive of threshold requirements. No complications were observed. This study failed, however, to document and standardize anesthetic technique or physiologic variables (pH, Pco_2, Po_2, body temperature, serum potassium) known to affect cardiac pacing thresholds (69). Kelly and colleagues (11) confirmed the findings of Berliner et al. (10) in cardiac surgical patients undergoing cardiopulmonary bypass. Furthermore, they measured multiple physiologic parameters that they correlated with NTP thresholds. The results demonstrate that NTP can be an effective alternative in this patient population. While NTP baseline ma were similar to those of healthy volunteers in Falk's initial work (6), NTP thresholds after chest wall closure were significantly elevated and approached the maximal unit output (140 ma) in some. A gradual return toward preoperative NTP thresholds was observed in the immediate postoperative period (Figure 3). Increases in cardiac output and core temperature were the only measured variables related to significant increases in current thresholds, with increasing age and pump time being of borderline significance. No complications were observed, in contrast to the small but real risks associated with epicardial pacemakers (especially with prolonged use) (70,71) and emergent transvenous pacemaker placement (1–3). The initial work in children by Beland et al. (68) involved 22 patients undergoing elective cardiac surgical procedures, with pacing trials in 21 of these occurring after induction of general anesthesia and neuromuscular blockade. No further details of their anesthetic management were reported. Despite a wide range of ages in their study population (11 months to 18 years), current output requirements for capture did not correlate with age, weight, body surface area, chest circumference, anteroposterior chest diameter, or ar-

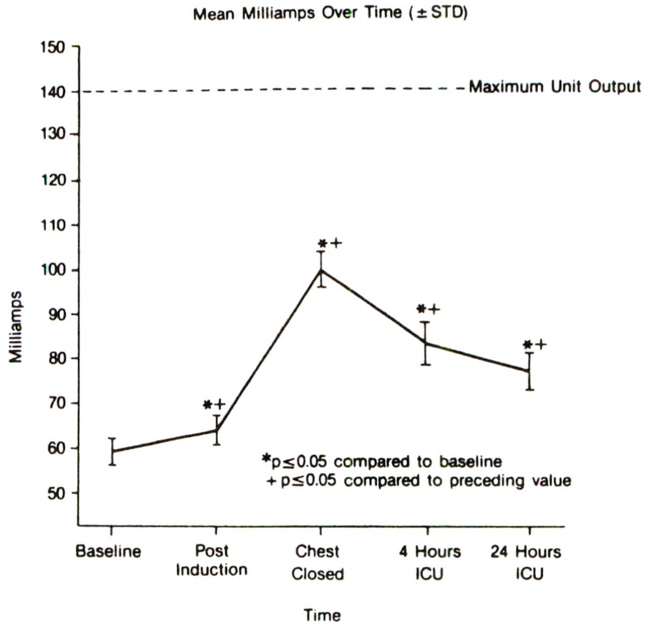


Figure 3. NTP thresholds during the operative course of cardiac surgical patients (reproduced with permission from *Anesthesiology* 1989, Vol. 70).

terial PO_2, Pco_2, or pH. Thresholds averaged between 51 and 63 ma, depending on the size of the transmitting electrodes utilized (68).

Previous investigators have evaluated the need for cardiac pacing in the setting of cardiac surgery. Vitello-Cicciu and associates (72) studied 100 consecutive adult patients undergoing coronary revascularization and showed that almost half required temporary epicardial pacing postoperatively, the majority during the first 48 hr. Age, previous myocardial infarction, and preoperative use of diuretics were significantly associated with the need for pacing in this study. In comparison, in a larger series of nearly 6,000 cardiac operations only 2.1% required permanent cardiac pacing postoperatively, the majority within 30 days of surgery. Eighty percent of the patients ultimately paced underwent primarily valvular surgery, with tricuspid valve procedures being most likely to require this modality. Other important variables demonstrated included preoperative conduction disturbances, advanced age, a densely calcified aortic annulus, and poor myocardial preservation (73).

Common operative scenarios in which NTP could prove useful include patients with transvenous pacemakers presenting for operation or pacemaker-related procedures. Intraoperative transvenous pacemaker malfunction is a rare, but well-described phenomenon and may be due to such events as electrocautery reprogramming (74), positive pressure ventilation (75), and sepsis with RV perforation (76). Nitrous oxide entrapment within the pacemaker generator pocket leading to interruption of anodal contact and pacemaker dysfunction has also been reported (77). Interestingly, the rate of false inhibition of permanent pacemakers due to extracorporeal shock wave lithotripsy appears minimal as long as the shock waves are delivered synchronously with the QRS complex (78). Availability of the specific pacemaker's programming unit in the operating room as well as efforts to minimize electrosurgical and monitoring interference with the pacemaker circuit decrease the potential for morbidity and mortality. NTP application in a standby demand mode adds significantly to patient safety in this circumstance, and its use for overdrive suppression of runaway pacemakers (63), bradycardia due to generator failure (4,40), and during pacemaker procedures (4) have all been reported. Similar prophylactic use of NTP during cardioversion for atrial tachyarrhythmias (4,65) and passage of pulmonary artery catheters in patients with left bundle-branch block (LBBB) (67) appears appropriate. Whereas the risk of complete heart block in the latter circumstance is minimal for patients with old or indeterminate-age LBBB (79), previous records are often unavailable or incomplete. NTP standby use in this case would add no additional risk, minimal cost, and superior safety.

Two other situations warrant consideration for NTP use by the anesthesiologist. The first involves acute inferior myocardial infarctions with conduction disturbances and suspected RV involvement. Prophylactic transvenous pacing in this instance is seldom indicated due to the temporary (that is, ischemic) nature of the conduction delay. When it does become necessary, however, a high incidence of ventricular fibrillation has been reported (80). There has been, in addition, one case reporting failure of RV endocardial pacing in acute RV infarction where NTP was subsequently used successfully (41). The ability of NTP to activate larger surface areas of both ventricles may partially explain this case. Because patients with acute inferior myocardial infarction may present for emergency procedures, the advantages of NTP in this setting are attractive. Another special circumstance is post-countershock pulseless rhythms. Defibrillation has been known occasionally to cause pre-existing endocardial pacemakers to fail (81). Defibrillation also results in asystole or pulseless rhythms more than 50% of the time. Animal studies (82) show immediate RV endocardial pacing by itself to be of no benefit compared with CPR and epinephrine for this problem. NTP's larger surface area for stimulus transmission may again have some theoretical advantages for this disorder.

Conclusion

NTP represents an effective alternative for the temporary management of hemodynamically significant bradyarrhythmias in the operating room. Along with atropine, it forms the cornerstone for current ACLS management of bradycardia, with current data suggesting NTP to be of value when used early in witnessed bradyasystolic cardiac arrest. Efficacy in patients undergoing general anesthesia and after cardiac surgery has now been clearly demonstrated. NTP's superior safety compared with other emergent pacing alternatives and its ease of use by medical and paramedical personnel make it the emergency pacemaker of choice for acute stabilization of patients who require pacing. Further, more definitive treatment of the underlying disturbance after initial use of NTP can subsequently be undertaken in a more controlled environment. In addition, NTP may prove efficacious for prophylactic use in patients with pre-existing pacemakers and patients with LBBB undergoing central hemodynamic monitoring. Lastly, NTP may occasionally be useful for elective overdrive suppression of hemodynamically stable tachyarrhythmias.

We thank Robin Moore for technical assistance and Faith McLellan and Dr. Donald Prough for editorial advice.

References

1. Austin JL, Preis LK, Crampton RS, Beller GA, Martin RP. Analysis of pacemaker malfunction and complications of temporary pacing in the coronary care unit. Am J Cardiol 1982; 49:301–6.
2. Hynes JK, Holmes DR Jr, Harrison CE. Five-year experience with temporary pacemaker therapy in the coronary care unit. Mayo Clin Proc 1983;58:122–6.
3. Abinader EG, Sharif D, Malouf S, Goldhammer E. Temporary transvenous pacing: analysis of indications, complications and malfunctions in acute myocardial infarction versus noninfarction settings. Isr J Med Sci 1987;23:877–80.
4. Zoll PM, Zoll RH, Falk RH, Clinton JE, Eitel DR, Antman EM. External noninvasive temporary cardiac pacing: clinical trials. Circulation 1985;71:937–44.
5. Syverud SA, Hedges JR, Dalsey WC, Gabel M, Thomson DP, Engel PJ. Hemodynamics of transcutaneous cardiac pacing. Am J Emerg Med 1986;4:17–20.
6. Falk RH, Zoll PM, Zoll RH. Safety and efficacy of noninvasive cardiac pacing. N Engl J Med 1983;309:1166–8.
7. Madsen JK, Meibom J, Videbak R, Pedersen F, Grande P. Transcutaneous pacing: experience with the Zoll noninvasive temporary pacemaker. Am Heart J 1988;116:7–10.
8. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 1986; 255:2905–89.
9. Luck JC, Grubb BP, Artman SE, Steckbeck RT, Markel ML. Termination of sustained ventricular tachycardia by external noninvasive pacing. Am J Cardiol 1988;61:574–7.
10. Berliner D, Okun M, Peters RW, Carliner NH, Plotnick GD, Fisher ML. Transcutaneous temporary pacing in the operating room. JAMA 1985;254:84–6.
11. Kelly JS, Royster RL, Angert KC. Efficacy of noninvasive transcutaneous cardiac pacing in patients undergoing cardiac surgery. Anesthesiology 1989;70:747–51.
12. Zoll PM. Resuscitation of the heart in ventricular standstill by external electric stimulation. N Engl J Med 1952;247:768–71.
13. Zoll PM, Linenthal AJ, Norman LR, Belgard AH. Treatment of Stokes-Adams disease by external electric stimulation of the heart. Circulation 1954;9:482–93.
14. Zoll PM, Linenthal AJ, Norman LR, Paul MH, Gibson W. External electric stimulation of the heart in cardiac arrest: Stokes-Adams disease, reflex vagal standstill, drug-induced standstill, and unexpected circulatory arrest. Arch Intern Med 1955;96:639–53.
15. Zoll PM, Linenthal AJ, Norman LR, Paul MH, Gibson W. Treatment of unexpected cardiac arrest by external electric stimulation of the heart. N Engl J Med 1956;254:541–6.
16. Leatham A, Cook P, Davies JG. External electric stimulator for treatment of ventricular standstill. Lancet 1956;12:1185–9.
17. Hazard PB, Benton C, Milnor JP. Transvenous cardiac pacing in cardiopulmonary resuscitation. Crit Care Med 1981;9:666–8.
18. Syverud SA, Dalsey WC, Hedges JR, Hanslits ML. Radiologic assessment of transvenous pacemaker placement during CPR. Ann Emerg Med 1986;15:131–7.
19. Zoll PM. Noninvasive temporary cardiac pacing. J Electrophys 1987;1:156–61.
20. Vargese PJ, Bren G, Ross A. Electrophysiology of external pacing: a comparative study with endocardial pacing (abstr). Circulation 1982;66(suppl II):II-349.
21. Heller MB, Kaplan RM, Peterson J, Paris PM, Ilkhanipour K, Stewart RD. Comparison of performance of five transcutaneous pacing devices (abstr). Ann Emerg Med 1987;16:493.
22. Falk RH, Ngai STA, Kumaki DJ, Rubinstein JA. Cardiac activation during external cardiac pacing. PACE 1987;10(Pt. I):503–6.
23. Prochaczek F, Gaiecka J, Machalski M, Jarczok K, Becker A. Diagnostic transcutaneous cardiac pacing examination of the ventriculo-atrial conduction (abstr). PACE 1988;11(suppl):856.
24. Feldman MD, Zoll PM, Aroesty JM, Gervino EV, Pasternak RC, McKay RG. Hemodynamic response to noninvasive external cardiac pacing. Am J Med 1988;84(Pt. 1):395–400.
25. Geddes LA, Voorhees WD III, Babbs CF, Sisken R, Deford J. Precordial pacing windows. PACE 1984;7(Pt. V):806–12.
26. Falk RH, Ngai STA. External cardiac pacing: influence of electrode placement on pacing threshold. Crit Care Med 1986; 14:931–2.
27. Geddes LA, Babbs CF, Voorhees WD III, Foster KS, Aronson AL. Choice of the optimum pulse duration for precordial cardiac pacing: a theoretical study. PACE 1985;8:862–9.
28. Niemann JT, Rosborough JP, Garner D, Aronson AL, Criley JM. External noninvasive cardiac pacing: a comparative hemodynamic study of two techniques with conventional endocardial pacing. PACE 1984;7:230–6.
29. Madsen JK, Pedersen F, Grande P, Meibom J. Normal myocardial enzymes and normal echocardiographic findings during noninvasive transcutaneous pacing. PACE 1988;11:1188–93.
30. Trigano JA, Remond JM, Mourot F, Birkui P, Raybaud C. Left ventricular pressure during transcutaneous pacing (abstr). PACE 1988;11(suppl):856.
31. Murdock DK, Moran JF, Speranza D, Loeb HS, Scanlon PJ. Augmentation of cardiac output by external cardiac pacing: pacemaker-induced CPR. PACE 1986;9(Pt. I):127–9.
32. Zoll PM, Zoll RH, Belgard AH. External noninvasive electric stimulation of the heart. Crit Care Med 1981;9:393–4.
33. Voorhees WD III, Foster KS, Geddes LA, Babbs CF. Safety factor for precordial pacing: minimum current thresholds for pacing and for ventricular fibrillation by vulnerable period stimulation. PACE 1984;7(Pt. I):356–60.
34. Syverud SA, Dalsey WC, Hedges JR, et al. Transcutaneous cardiac pacing: determination of myocardial injury in a canine model. Ann Emerg Med 1983;12:745–8.
35. Dalsey WC, Syverud SA, Hedges JR. Emergency department use of transcutaneous pacing for cardiac arrests. Crit Care Med 1985;13:399–401.
36. Beland MJ, Hesslein PS, Rowe RD. Ventricular tachycardia related to transcutaneous pacing. Ann Emerg Med 1988;17: 279–81.
37. Barthell E, Troiano P, Stueven HA, Schwartz J, Thompson B. Successful resuscitation using transcutaneous cardiac pacing. Resuscitation 1987;15:209–16.
38. Chan W, Warren RJ, Hunt D. Emergency external cardiac pacing in life-threatening bradyarrhythmias. Med J Aust 1986; 144:40–1.
39. Dalsey WC, Syverud SA, Ross DS, Yeiser F, Carducci B. Transcutaneous cardiac pacing (letter). Ann Emerg Med 1984; 13:410–1.
40. McNeil EL. Successful resuscitation using external cardiac pacing. Ann Emerg Med 1985;14:1230–2.

41. Little T. External cardiac pacing in right ventricular infarction. Ann Emerg Med 1988;17:640–2.
42. O'Toole KS, Paris PM, Heller MB, Stewart RD. Emergency transcutaneous pacing in the management of patients with bradyasystolic rhythms. J Emerg Med 1987;5:267–73.
43. Paris PM, Stewart RD, Kaplan RM, Whipkey R. Transcutaneous pacing for bradyasystolic cardiac arrest in prehospital care. Ann Emerg Med 1985;14:320–3.
44. Falk RH, Jacobs L, Sinclair A, Madigan-McNeil C. External noninvasive cardiac pacing in out-of-hospital cardiac arrest. Crit Care Med 1983;11:779–82.
45. Eitel DR, Guzzardi LJ, Stein SE, Drawbaugh RE, Hess DR, Walton SL. Noninvasive transcutaneous cardiac pacing in prehospital cardiac arrest. Ann Emerg Med 1987;16:531–4.
46. Feldman J, McNeil CM. Prehospital transcutaneous pacing for symptomatic bradycardia: the Boston EMS Experience (abstr). PACE 1988;11(suppl):857.
47. Jaggarao NSV, Heber M, Grainger R, Vincent R, Chamberlain DA. Use of an automated external defibrillator-pacemaker by ambulance staff. Lancet 1982:2:73–5.
48. Hedges JR, Syverud SA, Dalsey WC, Feero S, Easter R, Schultz B. Prehospital trial of emergency transcutaneous cardiac pacing. Circulation 1987;76:1337–43.
49. Barthell E, Troiano P, Olson D, Stueven HA, Hendley G. Prehospital external cardiac pacing: a prospective, controlled clinical trial. Ann Emerg Med 1988;17:1221–6.
50. White JM, Nowak RM, Martin GB, Best R, Carden DL, Tomlanovich MC. Immediate emergency department external cardiac pacing for prehospital bradyasystolic arrest. Ann Emerg Med 1985;14:298–302.
51. Olson CM, Jastremski MS, Smith RW, Tyndall GJ, Montgomery GF, Daye MC. External cardiac pacing for out-of-hospital bradyasystolic arrest. Am J Emerg Med 1985;3:129–31.
52. Clinton JE, Zoll PM, Zoll R, Ruiz E. Emergency noninvasive external cardiac pacing. J Emerg Med 1985;2:155–62.
53. Knowlton AA, Falk RH. External cardiac pacing during in-hospital cardiac arrest. Am J Cardiol 1986;57:1295–8.
54. Noe R, Cockrell W, Moses HW, Dove JT. Batchelder JE. Transcutaneous pacemaker use in a large hospital. PACE 1986;9(Pt. I):101–4.
55. Jansen W, Weidman B, Tauchert M. Transcutaneous cardiac stimulation on the intensive care unit (abstr). PACE 1988;11 (suppl):857.
56. Worley SJ, Bride WM. External transthoracic pacing in patients with acute myocardial infarction. In: Califf RM, Wagner GS, eds. Acute coronary care. Boston: Martinus Nijhoff Publishing, 1987:191–201.
57. Syverud SA, Dalsey WC, Hedges JR. Transcutaneous and transvenous cardiac pacing for early bradyasystolic cardiac arrest. Ann Emerg Med 1986;15:121–4.
58. Estes NAM III, Deering TF, Han EH, et al. Noninvasive termination of sustained supraventricular and ventricular tachycardia with external cardiac programmed stimulation (abstr). J Am Coll Cardiol 1987;9:200A.
59. Luck JC, Davis D. Termination of sustained tachycardia by external noninvasive pacing. PACE 1987;10:1125–9.
60. Barold SS, Falkoff MD, Ong LS, Heinle RA. Termination of ventricular tachycardia by transcutaneous cardiac pacing. Am Heart J 1987;114:180–2.
61. Rosenthal ME, Stamato NJ, Marchlinski FE, Josephson ME. Noninvasive cardiac pacing for termination of sustained, uniform ventricular tachycardia. Am J Cardiol 1986;58:561–2.
62. Beaudry PR, Rosengarten MD, Nadeau L. Termination of ventricular tachycardia with transcutaneous cardiac pacing. Can Med Assoc J 1986;134:145–6.
63. Bluhm G, Sundstedt CD. Runaway pacemaker inhibited by external overdrive stimulation: a case report. PACE 1984;7(Pt. I):440–2.
64. Kenyon CJ, Aldinger GE, Joshipura P, Zaid GJ. Successful resuscitation using external cardiac pacing in beta adrenergic antagonist-induced bradyasystolic arrest. Ann Emerg Med 1988;17:711–3.
65. Sharkey SW, Chaffee V, Kapsner S. Prophylactic external pacing during cardioversion of atrial tachyarrhythmias. Am J Cardiol 1985;55:1632–4.
66. Kay MM, Kranz JM. External transcutaneous pacemaker for profound bradycardia associated with spinal cord trauma. Surg Neurol 1984;22:344–6.
67. Buran MJ. Transcutaneous pacing as an alternative to prophylactic transvenous pacemaker insertion (letter). Crit Care Med 1987;15:623–4.
68. Beland MJ, Hesselein PS, Finlay CD, Faerron-Angel JE, Williams WG, Rowe RD. Noninvasive transcutaneous cardiac pacing in children. PACE 1987;10:1262–70.
69. Dohrmann ML, Goldschlager NF. Myocardial stimulation threshold in patients with cardiac pacemakers: effect of physiologic variables, pharmacologic agents, and lead electrodes. Cardiol Clin 1985;3:527–37.
70. Hoidal CR. Pericardial tamponade after removal of an epicardial pacemaker wire. Crit Care Med 1986;14:305–6.
71. Oldershaw PJ, Sutton MG, Ward D, Jones S, Miller GAH. Ten-year experience of 359 epicardial pacemaker systems: complications and results. Clin Cardiol 1982;5:515–9.
72. Vitello-Ciccia JM, Brown MM, Lazar HL, McCabe C, McCormick JR, Roberts AJ. Profile of patients requiring the use of epicardial pacing wires after coronary artery bypass surgery. Heart Lung 1987;16:301–5.
73. Goldman BS, Hill TJ, Weisel RD, et al. Permanent cardiac pacing after open heart surgery: acquired heart disease. PACE 1984;7(Pt. I):367–71.
74. Shapiro WA, Roizen MF, Singleton MA, Morady F, Bainton CR, Gaynor RL. Intraoperative pacemaker complications. Anesthesiology 1985;63:319–22.
75. Thiagarajah S, Azar I, Agres M, Lear E. Pacemaker malfunction associated with positive-pressure ventilation. Anesthesiology 1983;58:565–6.
76. Lyons C. Sepsis and pacemaker malfunction. Arch Intern Med 1982;142:1931.
77. Lamas GA, Rebecca GS, Braunwald NS, Antman EM. Pacemaker malfunction after nitrous oxide anesthesia. Am J Cardiol 1985;56:995.
78. Langberg J, Abber J, Thuroff JW, Griffin JC. The effects of extracorporeal shock wave lithotripsy on pacemaker function. PACE 1987;10:1142–6.
79. Morris D, Mulvihill D, Lew WYW. Risk of developing complete heart block during bedside pulmonary artery catheterization in patients with left bundle-branch block. Arch Intern Med 1987;147:2005–10.
80. Sclarovsky S, Zafrir N, Strasberg B, et al. Ventricular fibrillation complicating temporary ventricular pacing in acute myocardial infarction: significance of right ventricular infarction. Am J Cardiol 1981;48:1160–6.
81. Owen PM. The effects of external defibrillation on permanent pacemakers. Heart Lung 1983;12:274–7.
82. Niemann JT, Haynes KS, Garner D, Rennie CJ III, Jagels G, Stormo O. Postcountershock pulseless rhythms: response to CPR, artificial cardiac pacing, and adrenergic agonists. Ann Emerg Med 1986;15:112–20.

ANESTH ANALG 1989;69:239–41

Clinical Reports

Autotransfusor Removal of Fentanyl from Blood

Leland H. Hanowell, MD, John H. Eisele JR, MD, and Evangeline V. Erskine, BS

Key Words: TRANSFUSION—autotransfusor.
ANALGESICS—fentanyl.

The removal of narcotics from blood processed by commercially available autoinfusion devices, though not previously investigated, would be anticipated given the removal of significant quantities of serum during cell processing. Therefore, we attempted to determine if significant quantities of the narcotic fentanyl are removed from intraoperatively harvested blood during saline washing of red cells before autologous transfusion.

Methods

Six patients gave informed consent for this project, which was approved by the Institutional Human Studies Committee. The autotransfusion device (Autotrans BT 795, Dideco, Englewood, CO) was used in a conventional manner to salvage blood for reinfusion from the surgical field during operation on the spine. Heparinized saline solution was infused through the distal tip of the suction cannula in the surgical field to ensure anticoagulation of harvested blood, which was collected in a cardiotomy reservoir. A standard 1000 mL normal saline solution wash was used to process cells during centrifugal separation, yielding approximately 225 mL of packed red blood cells for reinfusion. The serum, heparinized saline, and normal saline separated from the cells were collected in a container for subsequent radioimmunoassay. Red cells retained in the centrifuged bowl of the cell saver were transferred to blood infusion bags without preservative. As observed in Figure 1, samples were collected from the reservoir and the discarded wash container. Hematocrit was measured by capillary tube centrifugation. Samples for fentanyl radioimmunoassay were centrifuged, and the supernatant was stored at 4°C. Patients 1 to 4 received fentanyl to supplement inhalational anesthesia. Blood collected from Patients 5 and 6 was studied by injecting the reservoir with fentanyl to yield the fentanyl concentrations shown in Table 1.

To evaluate the influence of the autotransfusor itself on fentanyl, a saline test preparation without blood was used to measure the fentanyl removed by the autoinfusion device. Saline solution (700 mL) was substituted for blood, and a known quantity of fentanyl (10 μg) was added to the reservoir bowl, followed by standard processing with a 1000-mL saline wash, as used for the patient collections. The saline in the reservoir was thus processed in the same way as blood from patient collections.

Radioimmunoassay of fentanyl concentrations (RIA, Janssen Pharmaceuticals, Piscataway, NJ) was performed using a Beckman scintillation counter. Standard curves were prepared with concentrations of serum, saline, and heparin in proportions equivalent to those of the specimen collection site. Removal of fentanyl from the reservoir for human subjects and saline trials were determined by expressing the amount of fentanyl collected in the wash container (mL collected multiplied by fentanyl concentration) as a percentage of the fentanyl in the reservoir (mL reservoir volume multiplied by fentanyl concentration).

Results

Table 1 shows the volume and hematocrit values of blood harvested from the surgical field. Fentanyl concentrations are given for samples from the reser-

---

Received from the Department of Anesthesiology, University of California, Davis Medical Center–Sacramento, Sacramento, CA. Accepted for publication November 1, 1988.

Address correspondence to Dr. Hanowell, Department of Anesthesiology, University of California, Davis Medical Center—Sacramento, 2315 Stockton Blvd., Sacramento, CA 95817.

©1989 by the International Anesthesia Research Society

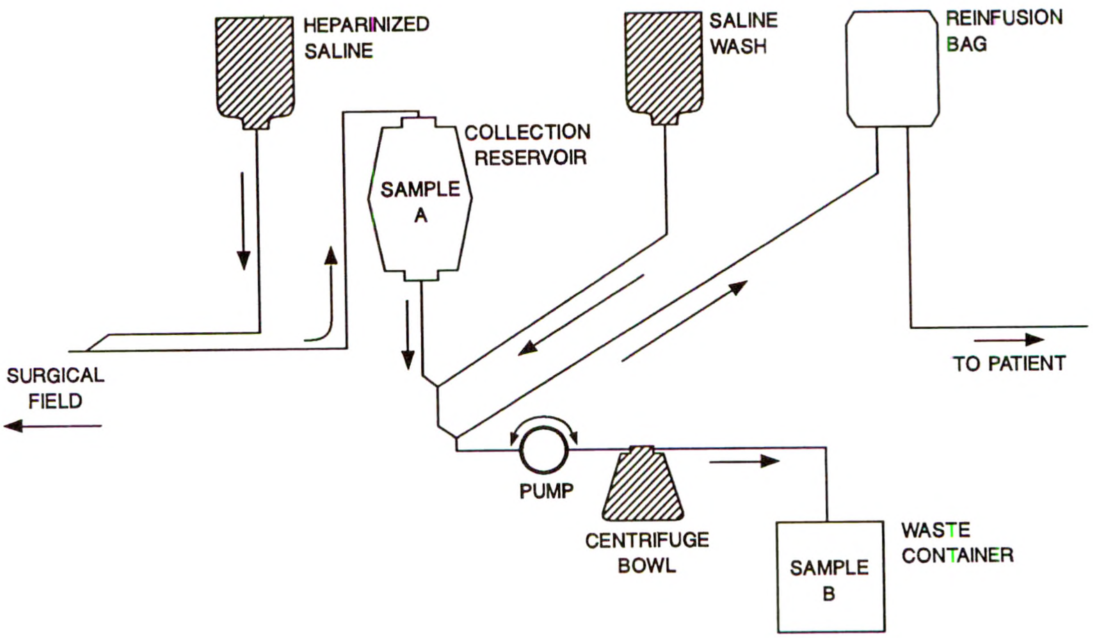


Figure 1. The autoinfusion system is diagrammed to show the sampling sites. Sample A is blood from the reservoir, and sample B is serum and saline collected during cell washing.

Table 1. Cell-Saver data: Human Subjects

	Volume	HCT	Fentanyl (ng/mL)	
Pt#	Reservoir		Reservoir	Wash
1	525	14	18.8	5.95
2	700	22	16.0	4.35
3	575	14	12.1	2.35
4	800	22	47.8	25.8
5	900	14	41.8	14.0
6	1000	12	63.0	26.0

Fentanyl concentrations of the reservoir and discarded wash were measured by radioimmunoassay.

voir and the wash. Approximately equal partitioning of fentanyl between serum and red cells was assumed (1). An average (±SD) of 74 ± 21% of the fentanyl in the reservoir was removed during processing of harvested blood for reinfusion. Fentanyl concentrations measured during the saline trials, including those of saline "harvested" in the reinfusion bags (Figure 1) are presented in Table 2. An average of 78% of the amount of fentanyl present was removed from the saline preparations. Table 3 summarizes mean values for data from the human subjects and saline trials.

Table 2. Cell Saver Data: Saline Preparations

	Volume (mL)	Fentanyl Concentration (ng/mL)		
Trial #	Reservoir	Reservoir	Wash	Reinfusion Bag
1	700	12.9	5.19	1.81
2	700	11.7	4.35	1.68

Fentanyl concentrations were measured in the saline preparations. Note that fluid collected in the reinfusion bags had a low fentanyl concentration.

Table 3. Mean Values for Data Obtained from the Study of Intraoperatively Salvaged Blood and Subsequent Saline Preparations

	Mean Values ± SD	Samples (*n*)
Reservoir hematocrit	15 ± 4	6
Reservoir volume	743 ± 147	6
% fent removed (blood)	74 ± 21	6
% fent removed (saline)	78	2
Hematocrit reinfused	35 ± 13	6

Discussion

Increased interest in autologous blood transfusion has resulted in increased utilization of the Autotrans BT 795 autotransfusion device used in this study and similar devices. Autologous blood infusion requires either prior collection and storage of blood or processing of blood harvested from the surgical field for reinfusion. Previous studies described the quality of the product processed by conventional autoinfusion devices. Advantages of cell-saving in this fashion include the absence of citrate in the blood given to replace blood lost, thus avoiding potential hypocalcemia during rapid or extensive transfusion. Additionally, McShane et al. (2) noted that the level of 2,3-diphosphoglycerate was higher in autologous blood processed by the autoinfusor than that of bank blood. They also noted an alkalotic pH in the reinfused blood, whereas bank blood has an acid pH.

Mendel et al. (3) described what they believed was a lack of hematologic and biochemical consequence, based on measurements of blood electrolyte levels and arterial blood gas tensions in patients receiving large infusions of saved cells. Our studies, however, demonstrate that processing blood for reinfusion removes a significant percentage of fentanyl from harvested blood before reinfusion. Shanks et al. (4) noted a 7.2% augmentation in clearance of *d*-tubocurarine when blood loss was salvaged by the Cell Saver (Hemonetics, Braintree, Mass) during spine surgery. Although fentanyl has a larger volume of distribution than *d*-tubocurarine, it is highly bound to plasma protein. An increased clearance of fentanyl would similarly be expected when plasma is removed from blood. However, removal of 74% of fentanyl from 1 L of blood, given a blood volume of 5 L, would remove only 15% of fentanyl from the intravascular space. Because blood level of fentanyl is only a fraction of the tissue level of fentanyl, loss of fentanyl via the cell saver of a highly lipophyllic drug such as fentanyl would not have an appreciable pharmacologic effect.

Reduced concentrations of fentanyl in the saline preparations may indicate another route of elimination of fentanyl apart from cell washing. Perhaps adsorption of fentanyl to components of the cell-saving device occurs.

The data from this study add new information to the growing body of knowledge related to the use of devices that permit intraoperative autologous infusion of salvaged blood. The use of these devices is important for the safety of our patients. Potential clinical sequelae of our findings, including decreased fentanyl serum concentrations, should be considered in patients undergoing extensive autotransfusion of shed blood. A precise determination of the impact of the cell saver on pharmacokinetics would require further study of blood levels of narcotics and other drugs used during anesthesia.

References

1. Meuldermans WE, Hurkmans RM, Heykants JJ. Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. Arch Int Pharmacodyn Ther 1982;257:4.
2. McShane AJ, Power C, Jackson JF, et al. Autotransfusion: quality of blood prepared with a red cell processing device. Br J Anaesth 1987;59:1035–9.
3. Mendel L, Smith MF, Park GR. Lack of haematological and biochemical consequences following autologous blood transfusion. Anaesthesia 1986;41:1259–60.
4. Shanks CA, Avram MJ, Ronai AK, et al. The pharmacokinetics of d-tubocurarine with surgery involving salvaged autologous blood. Anesthesiology 1985;62:161–5.

Ulnar Train-of-Four Stimulation in Predicting Face Movement during Intracranial Facial Nerve Stimulation

Larry C. Ho, MD†, Gregory Crosby, MD*, Pennathur Sundaram, MD*,
Steven F. Ronner, PhD†, and Robert G. Ojemann, MD†

Key Words: NEUROMUSCULAR RELAXANTS, ATRACURIUM. MONITORS, TRAIN-OF-FOUR. ANESTHESIA, NEUROSURGERY—monitoring of cranial nerves.

Direct intracranial electrical stimulation of the facial nerve is used frequently in posterior fossa surgery to help identify cranial nerve roots (1). A problem encountered by the anesthesiologist is uncertainty as to the degree of muscle relaxation that is compatible both with reliable facial movement to facial nerve stimulation and patient immobility during a balanced anesthetic. Ulnar nerve stimulation with surface electrodes and observation of thumb adduction (train-of-four [TOF]) is used commonly to assess neuromuscular blockade clinically, but how TOF can be used to predict whether the face will move when the facial nerve is stimulated intracranially is unclear. Accordingly, we evaluated the hypothesis that a high degree of motor blockade as assessed by ulnar TOF does not preclude satisfactory facial nerve monitoring.

Methods

Six adult ASA physical status I–II patients without facial nerve dysfunction scheduled for resection of small (<2 cm) acoustic neuromas were studied. The study was sanctioned by the institutional human investigation committee. Each patient was lightly premedicated with diazepam and anesthesia was induced with thiopental and fentanyl or sufentanil. Tracheal intubation was facilitated with succinylcholine. No additional relaxants were given and at least 2–3 h elapsed between administration of succinylcholine and the start of the study. Anesthesia was maintained with nitrous oxide. isoflurane, and additional narcotics. The investigator was not involved in the care of the patient and clinical management decisions were made by the primary anesthetist. Evoked facial and thumb movements were assesssed by piezoelectric accelerometers. One accelerometer was securely placed over the thenar eminence; the fingers were firmly taped to a wrist board to prevent motion artifact. Standard surface electrodes were positioned over the ulnar nerve so that the distal positive electrode lay 5 cm proximal to the wrist crease. A second accelerometer was positioned over the patient's cheek ipsilateral to surgery at a point considered to be optimal for sensing both circumoral and circumorbital movements.

Once the intracranial portion of the facial nerve was accessible, baseline measurements of face and thumb responses (height of positive seismographic displacement) to supramaximal electrical stimulation were obtained and recorded on a strip-chart recorder. The facial nerve was stimulated intracranially by the surgeon with a 60-Hz constant voltage monopolar stimulator. The ulnar nerve was stimulated simultaneously with a standard 2-Hz constant current stimulator. After obtaining stable baseline measurements, the patient was given atracurium 0.2–0.5 mg/kg intravenously until the response to a 2-Hz supramaximal electrical stimulus of the ulnar nerve at the wrist was completely abolished. Thereafter the ulnar nerve was stimulated every 10 sec and the facial nerve was stimulated at 5-min intervals for the duration of the study. The primary anesthetist (who was unaware of accelerometry data) also observed the face and thumb for movement. This process was repeated until all four thumb twitches were present. Accelerometry data were analyzed at two points: reappearance of the first thumb twitch (point 1, ~90% block), and

---

Received from the *Anesthesia and †Neurosurgical Services of the Massachusetts General Hospital and the Departments of Anesthesia and Surgery, Harvard Medical School, Boston, Massachusetts. Accepted for publication March 1, 1989.

Dr. Ho's present address is: Department of Anesthesiology, University of California Irvine Medical Center, 101 City Drive South, Orange, CA 92668.

Address correspondence to Dr. Crosby, Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114.

©1989 by the International Anesthesia Research Society

return of the fourth thumb twitch (point 2, ~70% block) (2). The amplitude of each response was measured and data are expressed as percent recovery of baseline displacement amplitude.

Results

Although the facial response, assessed by accelerometry and simple observation, to direct facial nerve stimulation was abolished by administration of atracurium, it recovered 12 ± 1.1 min (mean ± SEM) before thumb twitches were detectable. More importantly, even when there was 90% block by ulnar TOF (point 1), movement of the face was clearly observable in every patient (confidence limit 65%) and the accelerometer response had recovered to 76 ± 12% of baseline amplitude. When ulnar TOF was consistent with a 70% block (point 2), the facial response was 87 ± 4% of baseline amplitude. Thus, facial movement was clearly present both by accelerometry and observation in all patients when the first twitch of the ulnar TOF was just reappearing.

Discussion

Muscle relaxants are used commonly during anesthesia for delicate intracranial procedures to ensure patient immobility. During procedures that require monitoring of facial nerve function, however, neuromuscular blockade could prevent an effective facial muscle response and lead to the erroneous conclusion that the structure stimulated was not a cranial nerve. Studies using extracranial stimulation indicate that there is a difference in sensitivity between the facial and ulnar TOF responses during blockade with non-depolarizing muscle relaxants (3–5). Relative to ulnar TOF, for example, facial TOF evoked by superficial electrodes placed over the extracranial portion of the facial nerve tends to underestimate the degree of neuromuscular blockade. That is, at a given level of blockade, the facial response is always stronger.

Based on such data and clinical experience, we anticipated that a satisfactory facial response to direct intracranial stimulation of the facial nerve could be obtained despite a weak ulnar TOF. The data support our hypothesis and indicate that during recovery from a nondepolarizing block: 1) facial movement to intracranial stimulation of the facial nerve precedes return of the ulnar TOF, and 2) at the earliest hint of ulnar TOF recovery, the facial twitch is already strong. These results are unlikely to be specific for atracurium, but probably apply to all nondepolarizing relaxants, even though the absolute time to recovery would obviously vary. Factors such as preoperative facial nerve dysfunction secondary to compression, characteristics of the stimulus, and methods of monitoring neuromuscular function could influence the results, however, so extrapolation to clinical conditions different from ours must be made cautiously. For instance, we compared the facial response to 60-Hz stimulation of the facial nerve to thumb TOF. While equivalent TOF or tetanic stimuli to the facial and ulnar nerves would provide a better basis for comparison, using TOF for direct facial nerve stimulation or 60-Hz tetanus to the ulnar nerve neither makes sense nor serves a useful purpose during these procedures. The neurosurgeon stimulates the facial nerve for anatomical purposes (i.e., to identify cranial nerves) while the anesthesiologist uses ulnar stimulation to assess neuromuscular function. Moreover, previous work suggests that the response to direct facial nerve stimulation at 2 Hz (i.e., a TOF) would also be more resistant than ulnar TOF to neuromuscular blockade (3–5).

Several methods of monitoring were considered for this study. These included evoked electromyography, force-displacement transducer recordings, and accelerometry. Accelerometry was chosen because it was already used routinely at our institution during cases requiring facial nerve monitoring, is noninvasive, applicable to both the face and the thumb (unlike a force-displacement transducer), is relatively insensitive to electrical interference, and appears to be gaining popularity as a clinical neuromuscular blockade monitor. Most importantly, however, accelerometry is a simple and reliable method of neuromuscular transmission monitoring that closely correlates with force-displacement transducer measurements (6).

It must be emphasized that this study provides no evidence for physiological differences between the facial and ulnar neuromuscular junctions. The study, however, provides a more rational basis for administering muscle relaxants during neurosurgical procedures requiring facial nerve stimulation and shows clearly that reliable facial nerve monitoring using evoked movement of the face as a guide is possible even when ulnar TOF indicates a high degree of neuromuscular blockade.

References

1. Moller AR, Jannetta RJ. Preservation of facial nerve during removal of acoustic neuromas. J Neurosurg 1984;61:757–60.
2. Ali HH, Savarese JJ. Monitoring of neuromuscular function. Anesthesiology 1976;45:216–49.

3. Stiffel P, Hameroff SR, Blitt CD, Cork RC. Variability in assessment of neuromuscular blockade. Anesthesiology 1980; 52:436–7.

4. Pathak D, Sokoll MD, Barcellos W, Kumar V. A comparison of the response of hand and facial muscles to nondepolarizing relaxants (abstract). Anesthesiology 1986;65:A–299.

5. Caffrey RR, Warren ML, Becker KE Jr. Neuromuscular blockade monitoring comparing the obicularis oculi and adductor pollicis muscles. Anesthesiology 1986;65:95–7.

6. Werner MU, Jensen E, Nielsen HK, Viby-Morgensen J. Assessment of the evoked acceleration response during recovery from vecuronium and atracurium induced block (abstract). Anesthesiology 1987;67:A–344.

Fifty-Seven Years Ago in

Anesthesia & Analgesia

H. Thoms: Walter Channing and the introduction of anesthesia in childbirth. Current Researches in Anesthesia and Analgesia: 1932;11:1–4.

The subject of this paper, Dr. Walter Channing, and the author, Dr. Herbert Thoms, were both important in the history of obstetrics and obstetrical anesthesia in the United States.

First, Dr. Channing. His claim to fame lies in the fact that it was he who was primarily responsible for the introduction and, above all, the acceptance of obstetrical anesthesia in the States. As Thoms points out, the use of anesthetics for delivery became generally accepted only after initially overwhelming opposition, characterized, as Thoms says, "by the denseness of its ignorance and the vehemence of its religious intolerance," was finally overcome. This opposition was overcome in Europe by Simpson, Professor of Obstetrics at the University of Edinburgh and introducer of chloroform. It was overcome in the U.S. by Channing.

Channing did not enjoy the international acclaim as scientist, teacher, and obstetrician that Simpson did, nor did he have the bombastic personality, much less the ego, of Simpson. Channing was the embodiment of the contemplative, persistent Yankee practitioner, quite capable of effectively but quietly revolutionizing clinical practice. Born in Rhode Island in 1786, Channing managed to get into Harvard. In his third year, however, he was thrown out because of his participation in a students' rebellion (not riot or protest, rebellion). Unfazed, he started the study of medicine in Philadelphia, Boston, London, and Edinburgh. Returning to Boston after receiving his M.D. degree in 1809 from the University of Pennsylvania, he entered the practice of obstetrics and, at the first meeting of the newly created Harvard medical faculty in 1816, was elected dean of its new medical school. On the staff of the Massachusetts General Hospital, Channing was also one of the founders of the Boston Lying-in Hospital (The "Lying-in" was dropped when the hospital became the Brigham and Womens Hospital, in part because no one any longer knew what "Lying-in" involved, and it sounded a bit racy). Almost immediately after the introduction in 1846 of ether for surgical anesthesia, Channing was giving ether to his obstetrical patients. Yes, *he* was giving it, not someone else. He was both obstetrician and anesthetist. In 1848 appeared his treatise on "Etherization in Childbirth," a classic in the history of medicine. The book came out while the controversy about anesthesia was still raging. The U.S. opposition, headed by Professor Charles D. Meigs in Philadelphia, who later was also to oppose Oliver Wendell Holmes' observation that puerperal fever was contagious, was powerful and convincing both on religious grounds (Genesis 3:16:"in sorrow thou shalt bring forth children") and on the theory that pain during labor was necessary and desirable for safety of mother and child. Simpson handled the religious objections in Britain by noting that, since God caused Adam to fall into a deep sleep for the costectomy that produced Eve (Genesis 2:21), anesthesia had already been divinely approved. (Apparently no one cited Psalm 127:3, "He giveth his beloved sleep," for the same purpose). Instead, Channing gained medical and popular approval of obstetrical anesthesia by providing hard facts and cold data to prove the efficacy and safety of ether anesthesia in childbirth, something neither Simpson nor anyone else in that era did so thoroughly and completely. Channing did this by reporting in his book data on 581 deliveries performed with ether anesthesia. Such data would be pooh-poohed today—no simultaneous controls of deliveries without anesthesia—but, after millenia of deliveries without anesthesia, control data were hardly needed. Thanks to Channing, obstetrical anesthesia was accepted in North America, not immediately, to be sure, but well before his death at age 90 in 1876.

Thoms affords richly deserved kudos for what Channing accomplished. Faintly ironic is that Thoms, soon to become Professor of Obstetrics and Gynecology at Yale University School of Medicine, was to achieve fame and a place in the pantheon of obstetrical history as an advocate of delivery without anesthesia, "natural childbirth." Thoms was the one to introduce, preach, prove, and popularize natural childbirth in the States, a technique originally developed in the U.K. by Grantley Dick-Read. Only much later, Lamaze was to further refine the concept of natural childbirth. Thoms was to a large extent responsible for having the pendulum swing away from the "everyone gets anesthetized (by ether or narcotics)" school of thought derived from Channing's work, to a more rational balance that offered women the choice of anesthesia or no anesthesia.

ANESTH ANALG 245
1989;69:245–9

Metabolism of Isoflurane in Patients Receiving Isoniazid

Ian S. Gauntlett, FFARCS, Donald D. Koblin, MD, PhD, Mark R. Fahey, MD, Krystyna Konopka, MD, PhD, Larry D. Gruenke, PhD, Lucy Waskell, MD, PhD, and Edmond I. Eger II, MD

Key Words: ANESTHETICS, VOLATILE—isoflurane. IONS, FLUORIDE. METABOLISM, ENZYME INDUCTION—metabolites. PHARMACOLOGY, ISONIAZID.

Administration of isoniazid in human patients may increase the metabolism of enflurane and increase serum fluoride ion concentrations (1) to levels that may transiently impair renal function (2,3). Although isoniazid therapy increases isoflurane metabolism in animals (4,5), its effects on the metabolism of this agent in human patients are unknown. We determined the breakdown of isoflurane in two patients treated with isoniazid by measuring the concentrations of fluoride ion and trifluoroacetic acid (TFA) in their serum, as well as fluoride ion, TFA, and organic fluoride levels in their urine before, during, and after administration of isoflurane.

Case Reports

Case 1

A 46-yr-old woman (weight 50 kg) in chronic renal failure secondary to diabetes mellitus was scheduled to receive a living donor-related renal transplant. Her therapy included continuous ambulatory peritoneal dialysis and daily doses of 10 units of lente insulin, subcutaneously, and 160 units of regular insulin in her dialysate fluid. Complications of her diabetes included retinopathy, gastrointestinal autonomic neuropathy, peripheral neuropathy, and a below-knee amputation. Appendectomy and thyroidectomy had been performed without anesthetic complications. Although previously treated with methyl dopa for hypertension, she required no medication to maintain a normal arterial blood pressure for 6 months before this admission. She had no evidence of hepatic impairment. Medications included thyroxine, metoclopramide, diphenoxylate/atropine (Lomotil), aluminium hydroxide, calcium, quinine, and folic acid.

A preoperative chest radiogram revealed an opacity in the right upper lobe of the lung, which was diagnosed as an old focus of tuberculosis. Because of the risk of reactivating the tuberculosis after immunosuppression for her impending renal transplant, daily isoniazid therapy (300 mg) was instituted and surgery delayed.

Renal transplantation was performed 6 days after commencement of isoniazid therapy. Anesthesia was induced with intravenous (IV) thiopental, and her trachea was intubated after paralysis with IV vecuronium. Anesthesia was maintained for 4 hr with 60% nitrous oxide, fentanyl (total 650 μg, IV) and isoflurane, 0.2–0.7% end-tidal concentration as measured by mass spectrometry. A total of 1.2 MAC-hr (the product of end-tidal isoflurane concentration as a fraction of minimum alveolar concentration [MAC] and the duration of administration in hours) was administered. Ventilation was controlled to maintain end-tidal P_{CO_2} between 32 and 37 mm Hg (measured by mass spectrometry).

Other drugs used intraoperatively included prednisone (100 mg, IV), azathioprine (200 mg, IV), mannitol (12.5 g, IV), furosemide (80 mg, IV), and cephazolin (1 g, IV). Blood glucose levels were controlled using a continuous infusion of insulin. We administered 0.5% bupivacaine (total 220 mg) with epinephrine (1:200,000) to provide intercostal and paravertebral nerve blockade (T7-L2) after skin closure. At the end of surgery, we reversed neuromuscular blockade

---

Supported in part by NIH grants GM35533 and POIAG3104, Veterans Administration merit review grants, and a grant from the Academic Senate of the University of California, San Francisco.

Received from the Departments of Anesthesia, University of California, San Francisco, CA, Veterans Administration Medical Center, San Francisco, CA, and the Liver Center, University of California, San Francisco, CA 94143. Accepted for publication March 1, 1989.

Address correspondence to Dr. Koblin, Anesthesiology Service (129), Veterans Administration Medical Center, 4150 Clement Street, San Francisco, CA 94121.

©1989 by the International Anesthesia Research Society

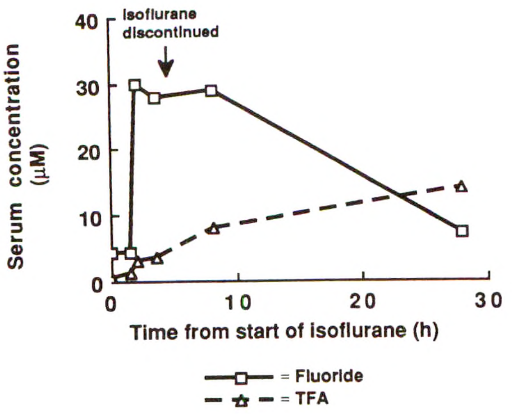


Figure 1. Serum concentrations of fluoride ion and trifluoroacetic acid (TFA) from Patient 1 are plotted against time from induction of anesthesia with isoflurane. Serum fluoride ion concentration reached approximately 30 µM between 2–8 hr. Concentrations of TFA increased to 14 µM by 24 hr.

with IV neostigmine and atropine, initiated spontaneous ventilation, and removed the endotracheal tube without complication.

The patient's intraoperative and postoperative course was uneventful, and the transplanted kidney functioned well. Urine production was >10 L over the first 48 hr. By postoperative day 3, blood urea nitrogen (BUN) had declined from a preoperative value of 60 to 5 mg/dL, and serum creatinine concentration from 10.8 to 0.7 mg/dL. Six months later, the graft was functioning well (BUN 14 mg/dL; serum creatinine 0.8 mg/dL) and showed no evidence of rejection.

Venous blood samples were obtained preoperatively at 90, 120, and 200 min and at 8 and 28 hr after beginning isoflurane administration. Urine samples were collected intraoperatively and postoperatively up to 48 hr, and the volumes quantitated over three separate time periods. The possibility of enhancement of isoflurane metabolism by isoniazid was not considered to represent a risk because of data from animal studies. The preoperative sample was obtained from a frozen sample held in the immunology laboratory.

Fluoride ion concentrations were measured using a fluoride ion electrode (6,7). Organic fluoride concentrations in urine were measured by a sodium fusion method (8), using a 90.4% efficiency for organic fluoride detection. Trifluoroacetic acid concentrations were measured using a gas chromatographic-mass spectrometry assay (9).

Serum fluoride ion concentration increased from 4.3 µM preoperatively to approximately 30 µM between 2 and 8 hr after commencing isoflurane administration (Figure 1). Serum TFA concentrations increased to 14 µM over the first 24 hr. No further blood samples were obtained after 24 hr (Figure 1). Average fluoride ion concentration in the urine approximately doubled over the 18-hr collection period after 6-hr intraoperative and postoperative sampling (Figure 2). The concentration then declined over the subsequent 24 hr. Urinary excretion of organic fluoride decreased over the 48-hr sampling period, whereas TFA excretion increased (Figure 2).

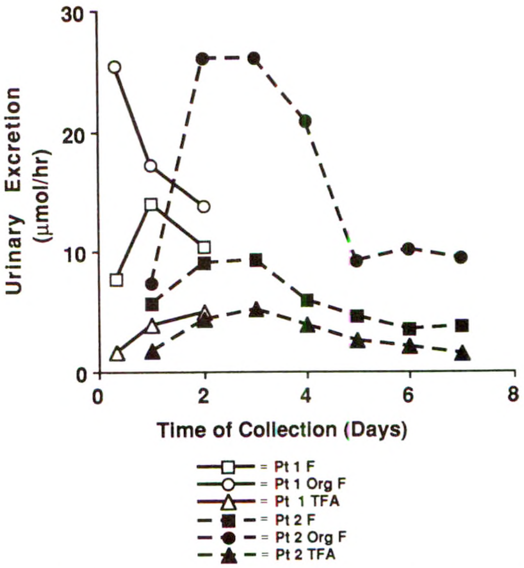


Figure 2. Urine excretion (µmol/hr^{-1}) of fluoride ion (F), organic fluoride (Org F), and trifluoroacetic acid (TFA) from both patients (Pt 1, 2) are plotted against time of urine collection after commencement of isoflurane administration.

Case 2

A 50-yr-old woman (weight 48 kg) was scheduled for construction of an ileal bladder to manage urinary incontinence and urinary tract infections resulting from a cerebrovascular accident. She had right-sided hemiparesis. Systemic lupus erythematosis and tuberculous meningitis were separately diagnosed in 1975, and treatment of the latter with isoniazid (300 mg, daily) was begun. At the time of admission for this surgery, the patient's medication included the same dose of isoniazid (13-yr therapy) and prednisone (5 mg, daily). There was no evidence of renal or hepatic impairment.

Anesthesia was induced with IV thiopental, and her trachea was intubated after paralysis with IV vecuronium. Anesthesia was maintained for 7 hr with isoflurane in oxygen (average end-tidal concentration 0.9%, measured by mass spectrometry), supplemented by fentanyl (total dose 550 µg, IV). A total of approximately 6 MAC-hr of isoflurane was admin-

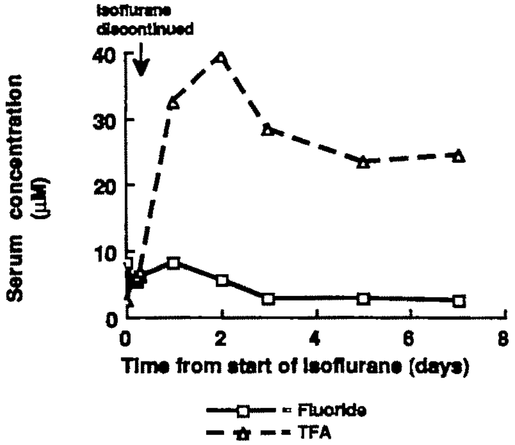


Figure 3. Serum concentrations of fluoride ion and trifluoroacetic acid (TFA) from Patient 2 are plotted against time from induction of anesthesia with isoflurane. Serum fluoride ion concentrations did not increase above the preoperative value. Concentrations of TFA increased to >30 µM by 24 hr and remained elevated for at least 7 days.

istered. Ventilation was controlled to maintain an end-tidal Pco_2 of 32–37 mm Hg (measured by mass spectrometry). At the time of surgery, we reversed neuromuscular blockade using IV neostigmine and glycopyrrolate, initiated spontaneous ventilation, and removed the endotracheal tube. Her postoperative course was complicated by fever and sepsis, which were successfully treated with ampicillin, gentamicin, and metronidazole.

Venous blood samples were obtained preoperatively at 150, 210, 300, 420 min and 24 hr after beginning isoflurane administration, and postoperatively on days 2, 3, 5, and 7. Urine samples were obtained every 24 hr after surgery until day 7. Serum fluoride and TFA concentrations and urinary excretion of fluoride ion, organic fluoride, and TFA were determined by the methods described in Case 1.

Serum fluoride ion concentration did not increase above the preoperative level of 8.3 µM, and declined to approximately 3 µM by day 3 (Fig. 3). Serum TFA concentrations were similar to those of the first patient over the anesthetic course, but increased to 32.4 µM by 24 hr (Figure 3). On day 7, these concentrations were still tenfold higher than the preoperative value. Fluoride ion concentration in urine increased over the first 3 days, then declined slowly (Figure 3). These values in this patient were slightly lower than those in the patient (Case 1) during the first postoperative 24 hr, but similar by 48 hr. Organic fluoride excretion reached a peak of 26 µmol/hr after 2 days remained at this level for 24 hr, then declined (Figure 2). Urinary TFA excretion peaked at day 3, then declined slowly (Figure 2). Values for both organic fluoride and TFA concentrations were similar to those of the first patient (Case 1) during the first 48 hr.

Discussion

Isoflurane is the least metabolized of the currently available volatile anesthetics (10). Healthy surgical patients exposed to an average of 3 MAC-hr of isoflurane have peak serum fluoride ion concentrations of 4–5 µM postoperatively (11). Healthy volunteers given approximately 7 MAC-hr isoflurane have postoperative serum fluoride ion concentrations of 1–4 µM (12).

Physiologic abnormalities or medications that promote the induction of hepatic enzymes may increase the metabolism of isoflurane. This has been demonstrated in a study of untreated diabetic rats (13) that, unlike treated diabetics (13,14), have enhanced isoflurane metabolism. Diabetes in our patient described in Case 1 had been well controlled with insulin before and during surgery. Serum concentrations of fluoride ion are higher (mean 6.6 µM) in morbidly obese patients given isoflurane (15), but neither of our patients was obese. We are unaware of any data suggesting induction of isoflurane metabolism by any of the concurrent medications taken by either patient.

We cannot explain the elevated preoperative serum fluoride concentration in Patient 2. The value of 8.3 µM is higher than previously reported concentrations of 1–2 µM in subjects with normal renal function (12,16). This patient was not taking any medication containing fluoride, and isoniazid is not known to affect preoperative serum fluoride levels in other patients (1). Patient 1 had a preoperative serum fluoride ion concentration of 4.3 µM, which is slightly higher than values of 3–3.5 µM previously reported in patients with poor renal function (16,17).

Patient 1 received a low total dose of isoflurane (1.2 MAC-hr) after only 6 days of isoniazid treatment, yet demonstrated a substantial increase in serum fluoride ion concentration. High-dose isoniazid pretreatment of similar duration in rats increases hepatic microsomal defluorination of isoflurane by only 168% (4), which would be insufficient to produce renal toxicity. The peak serum fluoride concentration of 30 µM in our patient (Figure 1) was nearly tenfold greater than the preoperative value, higher than any previously reported value after isoflurane administration, and comparatively prolonged, despite limited MAC-hr of exposure. Patient 2 had been treated with isoniazid for 13 years (the reason for such prolonged therapy is not clear) and was given five times the exposure (MAC-hr) to isoflurane given Patient 1, yet failed to demonstrate an increase in serum fluoride ion concentration above the preoperative value (Fig. 3).

Serum TFA concentrations were similar in both patients for the first 8 hr, but increased in Patient 2 (32.4 μM) by 24 hr (Fig. 3). This increase in TFA may be attributable to enzyme induction in Patient 2 as a result of long-term ingestion of isoniazid, although it is difficult to explain why serum fluoride ion concentration did not also increase. Although serum TFA concentrations were not measured after 24 hr in Patient 1, it is possible that the serum concentration continued to increase because the urine TFA excretion was still elevated at 48 hr, and was similar to that of Patient 2 (Figure 2).

Values for urinary excretion of fluoride ion and organic fluoride (Figure 2) in both patients were similar to excretion rates of fluoride ion (8 μmol/hr) and organic fluoride (54 μmol/hr) in healthy patients exposed to approximately 3 MAC-hr of isoflurane (11). Urinary excretion of TFA was similar in both patients over the first 48 hr of sampling, then excretion in Patient 2 slowly declined over the next 5 days. Values obtained in our patients were lower than those previously reported (18) in ASA physical status I patients given 2.4 MAC-hr of isoflurane. This discrepancy may be explained by a difference in study techniques. The earlier study (18) used thin-layer chromatography and estimated TFA concentration by combustion of the co-chromatographed nonionic metabolite of isoflurane. Consequently, other metabolites may have been erroneously identified as TFA, resulting in higher values. We used a gas chromatography-mass spectrometry assay specific for the detection of TFA (9).

Among patients given enflurane, approximately 50% treated with isoniazid have much higher serum fluoride ion concentrations than patients given no isoniazid (1). The apparent increase in fluoride ion concentration in only half of patients treated may be related to the genetically determined bimodal distribution of rapid and slow acetylation of isoniazid (1). We did not determine the acetylator phenotypes of our patients.

Although the serum fluoride ion concentration of 30 μM observed in Patient 1 is within the range associated with transient minor impairment of renal function (3), and although the toxicity of fluoride ion might be enhanced by pre-existing renal insufficiency, our patient suffered no adverse renal effects as assessed by BUN and creatinine or evidence of transplant rejection. We did not use more sensitive methods to detect minor functional impairment (e.g., ability to concentrate urine after vasopressin administration [3]) because it would have been difficult to separate any effects of fluoride ion from the variable function of the newly transplanted kidney. Low concentrations of isoflurane (as a supplement to nitrous oxide/opiate anesthesia) did not result in serum fluoride ion concentrations high enough to cause any clinically detectable impairment of renal function.

In summary, we measured serum concentrations of fluoride ion and TFA and urinary excretion of fluoride ion, TFA, and organic fluoride in two patients treated with isoniazid and exposed to isoflurane. The first patient, a diabetic renal transplant recipient, received isoniazid for 6 days preceding an anesthetic that included 1.2 MAC-hr of isoflurane. The patient developed relatively high (but clinically not significant) serum concentrations of fluoride ion and significant levels of TFA 2 days after anesthesia. Despite this elevation in serum fluoride ion concentration, no impairment of renal function occurred. The second patient had been medicated with isoniazid for 13 years, but showed no increase in serum fluoride concentration over preoperative values and only an increase in serum TFA concentration. Thus, although isoniazid may be associated with increased serum fluoride ion concentrations, this does not always occur. We speculate that the difference in findings between these patients may reflect the bimodal distribution of rapid and slow acetylation of isoniazid as suggested by Mazze et al. (1) for the metabolism of enflurane.

References

1. Mazze RI, Woodruff RE, Heerdt ME. Isoniazid-induced enflurane defluorination in humans. Anesthesiology 1982;57:5–8.
2. Mazze RI. Metabolism of the inhaled anaesthetics: implications of enzyme induction. Br J Anaesth 1984;56:27–41S.
3. Mazze RI, Calverly RK, Smith NT. Inorganic fluoride nephrotoxicity: prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 1977;46:265–71.
4. Rice SA, Sbordone L, Mazze RI. Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following isoniazid administration. Anesthesiology 1980;53:489–93.
5. Rice SA, Talcott RE. Effects of isoniazid treatment on selected hepatic mixed-function oxidases. Drug Metab Dispos 1979; 7:260–2.
6. Fry BW, Taves DR. Serum fluoride analysis with the fluoride electrode. J Lab Clin Med 1970;75:1020–5.
7. Koblin DD, Eger EI II, Johnson BH, Konopka K, Waskell L. I-653 resists degradation in rats. Anesth Analg 1988;67:534–8.
8. Soltis JJ, Gandolfi AJ. Detection of fluorinated anesthetic metabolites by sodium fusion. Anesth Analg 1980;59:61–4.
9. Gruenke LD, Waskell L. A gas chromatographic mass spectrometric method for the analysis of trifluoroacetic acid: application to the metabolism of halothane by in vivo preparations. Biomed Environ Mass Spectrom 1988;17:471–5.
10. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. The extent of metabolism of inhaled anesthetics in humans. Anesthesiology 1986;65:201–5.

11. Mazze RI, Cousins MJ, Barr GA. Renal effects and metabolism of isoflurane in man. Anesthesiology 1974;40:536–42.

12. Stevens WC, Eger EI II, Joas TA, Cornwell TH, White A, Dolan WM. Comparative toxicity of isoflurane, halothane, fluroxene and diethyl ether in human volunteers. Can Anaesth Soc J 1973;20:357–68.

13. Pantuck EJ, Pantuck CB, Conney AH. Effects of streptozotocin-induced diabetes in the rat on metabolism of fluorinated volatile anesthetics. Anesthesiology 1987;66:24–8.

14. Favreau LV, Malchoff DM, Mole JE, Schenkman JB. Responses to insulin by two forms of rat hepatic microsomal cytochrome P-450 that undergo major (RLM 6) and minor (RLM 5b) elevations in diabetes. J Biol Chem 1987;262:14319–26.

15. Strube PJ, Hulands GH, Halsey MJ. Serum fluoride levels in morbidly obese patients: enflurane compared with isoflurane anaesthesia. Anaesthesia 1987;42:685–9.

16. Carter R, Heerdt M, Acchiardo S. Fluoride kinetics after enflurane anesthesia in healthy and anephric patients and in patients with poor renal function. Clin Pharmacol Ther 1976;20:565–70.

17. Mazze RI, Sievenpiper TS, Stevenson J. Renal effects of enflurane and halothane in patients with abnormal renal function. Anesthesiology 1984;60:161–3.

18. Hitt BA, Mazze RI, Cousins MJ, Edmunds HN, Barr GA, Trudell JR. Metabolism of isoflurane in Fischer 344 rats and man. Anesthesiology 1974;40:62–7.

ANESTH ANALG
1989;69:250–5

Intravenous Injection of Liquid Halothane

R. Dwyer, FFARCS, and D. L. Coppel, FFARCS

Key Words: ANESTHETICS, VOLATILE—halothane. TOXICITY, HALOTHANE—pulmonary.

Halothane is a fluorinated hydrocarbon in common use as an inhalation anesthetic. Repeated exposure to halothane by inhalation may cause the rare complication of liver necrosis (probably by an allergic mechanism) (1). Otherwise, it is essentially nontoxic. In contrast, three cases have been described of the intravenous administration of halothane (2–4). All patients developed signs of a severe pulmonary vasculitis and two of the three died.

We describe below a case of self-injection with halothane with a fatal outcome despite intensive therapy. This is the only patient described in whom pulmonary artery pressures were measured and in whom treatment was attempted using the vasodilator epoprostenol (prostacyclin).

Case Report

A 52-yr-old, previously fit man injected himself with 3 mL of liquid halothane into a vein in his antecubital fossa. He immediately lost consciousness, then gradually recovered so that 40 min later he was drowsy, but oriented and in no respiratory distress. The odor of halothane could be detected on his breath.

One hour after injection, he developed central chest discomfort and a nonproductive cough. On auscultation of his chest, breath sounds were normal. Over the next hour he became dyspneic and slightly cyanosed; auscultation of his chest now revealed scattered rhonchi and rales. Furosemide 40 mg and aminophylline 250 mg were given intravenously by his family practitioner without improvement.

Three hours after injection he was admitted to the hospital with severe dyspnea, cyanosis, and hypotension (blood pressure was unrecordable). An arterial blood sample showed hypoxia ($\mathrm{Pa}o_2$ = 7.1 kPa [54 mm Hg] with a fraction of oxygen in inspired air [FI_{O_2}] of 0.5) and a metabolic acidosis (pH = 7.2, base excess = –17.4 mmol/L). $\mathrm{Pa}co_2$ was 2.9 kPa (22 mm Hg). Chest x-ray showed pulmonary edema. An electrocardiogram (ECG) indicated right heart strain with a deep S wave in lead 1 and Q wave in lead 111 (Figure 1).

He was given further doses of furosemide and aminophylline, sodium bicarbonate, and methylprednisolone 1 g. His condition deteriorated further and tracheal intubation and intermittent positive pressure ventilation (IPPV) were initiated. He remained seriously ill, needing colloid infusion and inotropes to maintain his systolic blood pressure at 80 mm Hg and 100% oxygen with 10 cm H_2O positive end-expiratory pressure (PEEP) to maintain $\mathrm{Pa}o_2$ at 10 kPa (76 mm Hg).

A pulmonary artery flotation catheter was inserted 7 hr after injection of halothane. This showed pulmonary artery (PA) pressures of 30/16 mm Hg with a pulmonary capillary wedge pressure (PCWP) of 8 mm Hg and central venous pressure (CVP) 8 mm Hg. Cardiac output measured by thermodilution showed a cardiac index (CI) of 2.4 $\mathrm{L \cdot min^{-1} \cdot m^{-2}}$; systemic vascular resistance (SVR) was 1237 $\mathrm{dyn \cdot sec \cdot cm^{-5}}$, pulmonary vascular resistance (PVR) 225 $\mathrm{dyn \cdot sec \cdot cm^{-5}}$, and shunt fraction 33% (Table 1).

An infusion of the vasodilator epoprostenol (prostacyclin) was started at a rate of 5 $\mathrm{ng \cdot kg^{-1} \cdot min^{-1}}$ in an attempt to reduce PVR and to improve cardiac output.

After commencement of epoprostenol, PVR decreased to 147 $\mathrm{dyn \cdot sec \cdot cm^{-5}}$, PA pressures to 18/7, and PCWP to 1 mm Hg. Cardiac index increased to 2.8 $\mathrm{L \cdot min^{-1} \cdot m^{-2}}$ and blood pressure reached 100 mm Hg systolic. $\mathrm{Pa}o_2$ was maintained at 10 kPa (76 mm Hg) (FI_{O_2} = 1.0) and shunt fraction was unchanged. Peripheral perfusion improved clinically and urine output remained satisfactory.

However, this improvement was short-lived and within 2 hr PVR again began to increase (to 203

Received from the Department of Clinical Anaesthesia, Royal Victoria Hospital, Belfast, Northern Ireland. Accepted for publication March 31, 1989.

Address correspondence to Dr. Dwyer, Department of Anaesthetics, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, UK.

©1989 by the International Anesthesia Research Society

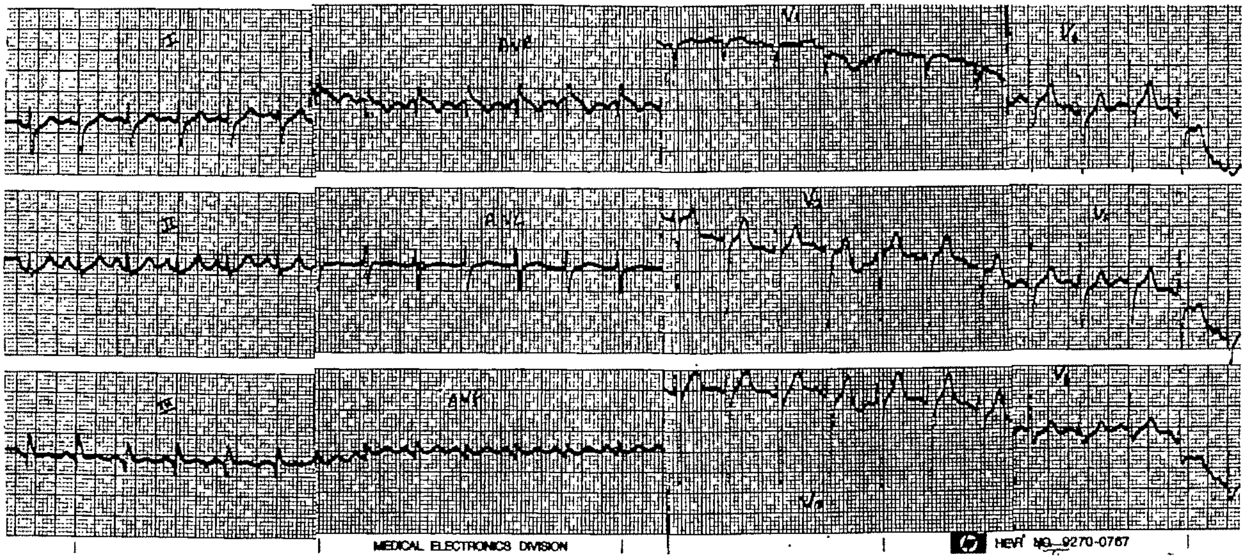


Figure 1. Electrocardiogram on admission showing signs of acute right heart strain.

dyn·sec·cm^{-5}) as did the PA pressures (to 28/6), despite increasing the infusion rate of epoprostenol to 10 ng·kg^{-1}·min^{-1}. Higher rates of epoprostenol infusion could not be tolerated because of hypotension.

Twenty-four hours after injection his chest x-ray showed severe pulmonary edema (Figure 2) despite the PCWP remaining low (6 cm H_2O). Pulmonary compliance had decreased and Pa_{O_2} decreased to 8 kPa (61 mm Hg) (FI_{O_2} = 0.8). Cardiac index was 2.0 L·min^{-1}·m^{-2} despite increasing doses of dopamine. Epoprostenol had been withdrawn for 1 hr and then reintroduced without significant effect. The ECG showed resolution of the signs of right heart strain but widespread S-T segment and T wave abnormalities (Figure 3, and after 48 hr, Figure 4). The site of halothane injection in the antecubital fossa was now markedly inflamed.

In an attempt to reduce pulmonary edema by removing fluid, ultrafiltration of blood was performed but had to be abandoned owing to resulting hypotension. Peritoneal dialysis was commenced to remove fluid in a more gradual manner and cooling to 34.5°C was introduced in an attempt to reduce O_2 consumption.

Over the next 72 hr oxygenation remained borderline even on 100% O_2 (Pa_{O_2} = 10 kPa [76 mm Hg]) (Table 2). High-frequency jet ventilation was attempted but this resulted in a sharp decrease in Pa_{O_2} and IPPV was recommenced with 15 cm H_2O PEEP. His PVR continued to increase steadily despite epoprostenol therapy, with PCWP and CVP both remaining around 10 mm Hg.

The pulmonary edema continued to progress despite achieving a negative fluid balance of 3.5 L over 24 hr by peritoneal dialysis. Seventy-two hours after halothane administration, PVR had increased to 419 dyn·sec·cm^{-5} and CI had decreased to 1.1 L·min^{-1}·m^{-2} despite dopamine 30 μg·kg^{-1}·min^{-1} (PCWP = 11 cm H_2O). Dobutamine was added to the dopamine infusion but the blood pressure dropped sharply on this mixture and the infusion was changed back to dopamine alone. Peripherally there was gross vasoconstriction.

For 48 hr after admission, urine output remained above 50 mL/hr despite hypotension. It then, however, decreased and by 72 hr after admission he was anuric. Although peritoneal dialysis continued, blood urea nitrogen (BUN) and creatinine levels increased steadily, and by day 6 BUN was 36 mmol/L and serum creatinine 613 mmol/L. Potassium was 6.1 mmol/L.

Liver function tests showed no gross abnormality during his illness: plasma levels of transaminases were not significantly elevated and bilirubin increased only slightly to 29 mmol/L by day 6. After the institution of hypothermia, hypoglycemia became a problem requiring the occasional administration of 50% dextrose.

Despite a white cell count of 20,000–30,000 during his illness, cultures of blood, bronchial secretions, urine, and central venous lines were sterile at all times and there was no other evidence of sepsis. His hemoglobin level remained above 11 g/dL throughout his illness.

Although there was a reduction in pulmonary edema by day 6, Pa_{O_2} was maintained at 11 kPa (84 mm Hg) only by 100% O_2 with 15 cm H_2O of PEEP;

Table 1. Cardiovascular Data Showing the Initial Effect of Epoprostenol in Lowering PVR and Subsequently the Progressive Rise in PVR Despite Epoprostenol

Time	BP (mm Hg)	CVP (mm Hg)	PA (mm Hg)	PCWP (mm Hg)	PVR (dyn·sec·cm^{-5})	SVR (dyn·sec·cm^{-5})	CI (L·min^{-1}·m^{-2} body surface area)	Comments
7.5 hr	91	8	30/16	8	225	1237	2.4	On dopamine
9 hr	105	3	18/7	1	147	1144	2.8	Add PGI_2 at 5 ng·kg^{-1}·min^{-1}
11 hr	103	3	28/6	0	203	1177	2.8	PGI_2 at 5 ng·kg^{-1}·min^{-1}
24 hr	90	8	26/15	6	274	1440	2.0	PGI_2 at 10 ng·kg^{-1}·min^{-1}
Day 2	90	14	31/22	13	325	1607	1.6	PGI_2 at 10 ng·kg^{-1}·min^{-1}
Day 3	120	13	28/18	11	419	2934	1.1	PGI_2 at 10 ng·kg^{-1}·min^{-1}
Day 6	100	12	—	—	—	—	—	PAFC removed

Abbreviations: BP, systolic blood pressure; CI, cardiac index; CVP, central venous pressure; PA, pulmonary artery pressures systolic/diastolic; PAFC, pulmonary artery flotation catheter; PCWP, pulmonary capillary wedge pressure; PGI_2, prostaglandin I_2 (epoprostenol); PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

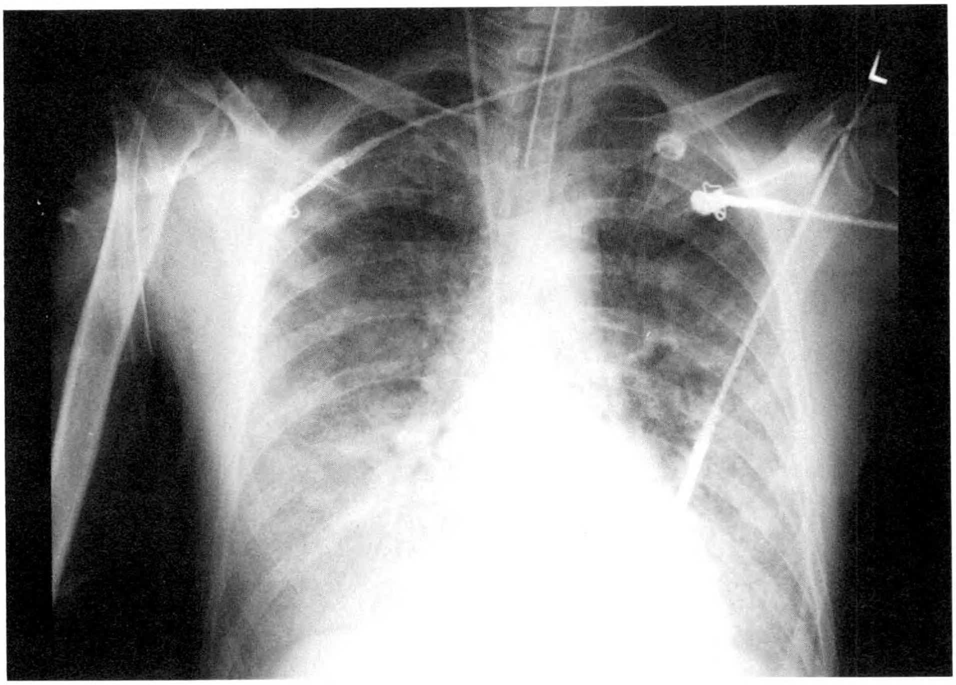


Figure 2. Chest x-ray 24 hr after injection of halothane showing widespread interstitial edema, most marked in the lower zones.

$Paco_2$ was 6.3 kPa (48 mm Hg). His BP remained around 100 mm Hg systolic with gross peripheral vasoconstriction and impalpable peripheral pulses, and CVP remained 12 cm H_2O. An isotope perfusion scan of his lungs was performed: this showed equal perfusion of both lungs with no gross perfusion defects, implying patency of the larger pulmonary arteries.

On day 6 a small pneumothorax developed: despite the rapid insertion of a chest drain and reexpansion of the lung he shortly afterwards developed bradycardia and asystolic cardiac arrest. Attempted resuscitation was unsuccessful.

Gross examination of the lungs at postmortem examination showed severe pulmonary edema and widespread pneumonic consolidation. Microscopically, most of the alveoli were filled with inflammatory cells (neutrophils, lymphocytes, proliferative type II pneumocytes, and macrophages) and fibrin. In some alveoli there was early organization. There were some small areas of hemorrhagic infarction associated with small organizing thrombi in the pulmonary arteries. Some small pulmonary vessels had areas of fibrinoid necrosis in their walls.

There were also small areas of hemorrhagic infarction in the spleen and pancreas. In the liver there was widespread acute centrizonal necrosis affecting most of the lobules, but there was no evidence of an inflammatory reaction. Brain, heart, and kidneys were essentially normal.

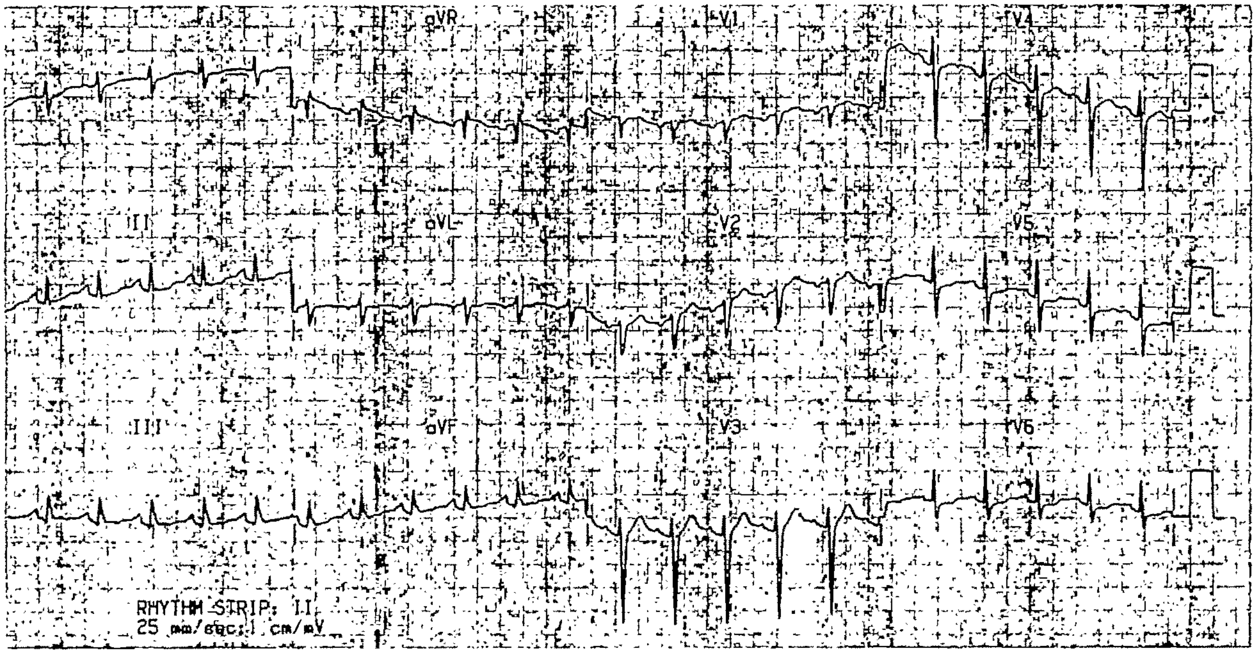


Figure 3. Electrocardiogram 24 hr after admission.

Table 2. Serial Arterial Blood Gas Values at Different Times after the Intravenous Injection of Halothane Demonstrating the Need for High Inspired Oxygen Concentrations to Maintain Adequate Oxygenation

Time	P_aO_2 [kPa (mm Hg)]	FI_{O_2}	P_aCO_2 [kPa (mm Hg)]	Comments
3 hr	7.1 (54)	0.5	2.9 (22)	O_2 by mask
7.5 hr	10.5 (80)	1.0	5.3 (40)	IPPV + 10 PEEP
9 hr	10.5 (80)	1.0	5.2 (39.5)	On PGI_2 at 5 ng· $kg^{-1}·min^{-1}$
24 hr	8.4 (74)	1.0	4.6 (35)	IPPV + 15 PEEP
Day 2	10.0 (76)	1.0	5.3 (40)	IPPV + 15 PEEP
Day 3	10.0 (76)	1.0	6.3 (48)	IPPV + 15 PEEP
Day 4	8.6 (65)	1.0	7.5 (57)	IPPV + 15 PEEP
Day 6	11.5 (87)	1.0	6.3 (48)	IPPV + 15 PEEP

Abbreviations: FI_{O_2}, fraction of oxygen in inspired air; IPPV, intermittent positive pressure ventilation; P_aCO_2, arterial CO_2 tension; PEEP, positive end-expiratory pressure (cm H_2O); P_aO_2, arterial oxygen tension.

Discussion

This case again illustrates the catastrophic effect of a small dose of halothane given intravenously. Our patient presented with the clinical picture of acute pulmonary edema and acute right heart failure due to damage to pulmonary vessels leading to hypoxia, vascular hypoperfusion, and death. This was secondary to pulmonary vasculitis and pulmonary edema caused by the direct effect of a bolus of halothane on small pulmonary vessels (as suggested by the fibrinoid necrosis in some vessel walls). Postmortem changes in other organs were nonspecific and probably related to the prolonged state of vascular hypoperfusion.

Pulmonary artery pressures have not been measured previously in humans after halothane injection. Pulmonary artery pressures in our patient showed a progressive increase after halothane injection stemming from increases in pulmonary vascular resistance. Severe pulmonary edema occurred rapidly after injection of halothane despite normal pulmonary capillary wedge pressures, implying capillary endothelial damage at an early stage.

Three previous cases of intravenous halothane administration have been described (2–4). All patients developed severe pulmonary edema within hours of administration leading to hypoxia and hypotension.

Two of these died after intravenous doses of 9 and 3 mL, respectively. Necropsy showed pulmonary edema in each case and, in the second case (with survival of 3 days), subpleural hemorrhages and inflammatory changes in branches of the pulmonary artery.

In the patient who survived (2), she received 2.5 mL of halothane intravenously. She had a slower onset of symptoms and did not require positive pressure ventilation until 48 hr after administration of the halothane. Her treatment was essentially supportive.

Oral ingestion of large amounts of halothane (35–250 mL) has been reported; two of these patients showed marked neurological, cardiac, and respira-

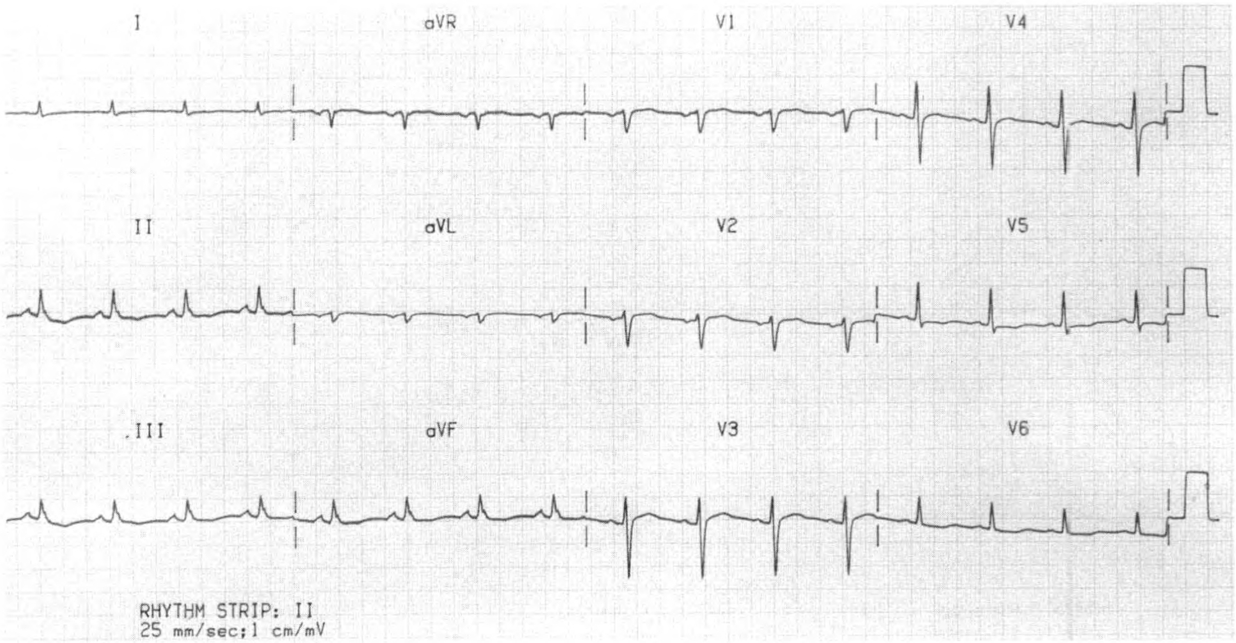


Figure 4. Electrocardiogram 48 hr after admission showing resolution of ECG evidence of right heart strain.

tory depression which reversed after elimination of the halothane, without long-term sequelae (5,6). A third patient, who had also ingested barbituates, died, presumably owing to cardiovascular and respiratory depression (7).

Dogs injected with halothane (8) develop diffuse pulmonary edema with focal areas of hemorrhage within 30 min of injection. Areas of focal hemorrhage are maximal in regions of the lung with the highest blood supply. Microscopically alveolar edema and alveolar and perivascular hemorrhage from congested capillaries are prominent. These changes are more marked in animals receiving larger doses of halothane. Changes are delayed and less extensive in animals given mechanical ventilation at the time of injection. In one surviving dog killed and examined 22 days after injection, histologic examination showed changes suggestive of healing pulmonary infarcts. In three dogs in which pulmonary artery pressures were measured, there were immediate and sustained increases after halothane injection averaging about 10 cm H_2O.

Thus intravenous halothane causes direct damage to the walls of smaller pulmonary vessels with an associated alveolar inflammatory response. Microthrombosis and infarction of vessels occur at a later stage and the clinical picture is similar to the adult respiratory distress syndrome (ARDS).

Epoprostenol is the exogenous form of prostacyclin (prostaglandin I_2) which is found normally in pulmonary vessels. It is a potent pulmonary vasodilator and inhibitor of platelet aggregation capable of lowering pulmonary vascular resistance and improving cardiac output in patients with pulmonary hypertension due to mitral valve disease (9) and primary pulmonary hypertension (10). Its use has not been described before to treat pulmonary hypertension due to toxic damage to pulmonary vessels. In our patient it initially reduced pulmonary vascular resistance and pulmonary artery pressures without increasing the shunt fraction, but this effect was short-lived and subsequently it had no effect on pressures in the pulmonary circulation.

Treatment of a patient after intravenous injection of halothane is essentially supportive. The study by Sandison et al. (8) suggests the importance of adequate oxygenation in limiting pulmonary damage. The patient's PCWP should be kept as low as possible, while maintaining adequate cardiac output and normal colloid osmotic pressure.

The place of steroids in the prevention and treatment of acute ARDS is controversial and unproved. Steroids are unlikely to be of benefit when endothelial cells have been damaged by the direct toxic effect of intravenous halothane.

The prognosis after administration of intravenous halothane seems to depend on the dose administered—the only patient reported who survived was the one who had the smallest dose, and in the study by Sandison et al. (8), dogs given higher doses had more extensive pathological changes. On the basis of the published cases to date, the mortality is extremely high.

If halothane is accidentally drawn into a plastic syringe, the plastic begins to dissolve making the plunger stick; this is a useful warning sign which should alert the anesthesiologist.

We would like to acknowledge the help of Dr. J. Crane, MRCPath, who performed the autopsy and examined the histologic specimens.

References

1. Neuberger J, Williams R. Halothane anaesthesia and liver damage. Br Med J 1984;289:1136–9.
2. Sutton J, Harrison GA, Hickie JB. Accidental intravenous injection of halothane. Br J Anaesth 1971;43:513–20.
3. Franks CR, Hudson PM, Rees AJ, Searle JF. Accidental intravenous halothane. Guy's Hosp Rep 1974;123:89–95.
4. Berman P, Tattersall M. Self-poisoning with intravenous halothane. Lancet 1982;1:340.
5. Curelaru I, Stanciu ST, Nicolau V, Fuhrer H, Iliescu M. A case of recovery from coma produced by the ingestion of 250 ml of halothane. Br J Anaesth 1968;40;283–8.
6. Wig J, Chrakravarty S, Krishnamurthy K, Mehta D. Coma following ingestion of halothane. Anaesthesia 1983;38:552–5.
7. Spencer JAE, Greene NM. Suicide by ingestion of halothane. JAMA 1968;205:702–3.
8. Sandison JW, Sivapragasam S, Hayes JA, Woo-Ming MO. An experimental study of pulmonary damage associated with intravenous injection of halothane in dogs. Br J Anaesth 1970;42:419–24.
9. Szczeklik J, Szczeklik A, Nizankowkski R. Prostacyclin for pulmonary hypertension. Lancet 1980;2:1076.
10. Jones DK, Higenbottam TW, Wallwork J. Treatment of primary pulmonary hypertension with intravenous epoprostenol (prostacyclin). Br Heart J 1987;57:270–8.

Etomidate Myoclonus and the Open Globe

James M. Berry, MD, and Robert G. Merin, MD

Key Words: ANESTHETICS, INTRAVENOUS—etomidate. ANESTHESIA, OPHTHALMOLOGIC.

Etomidate is a rapid-acting hypnotic, valued for its minimal respiratory and cardiovascular depression in comparison with thiopental. Known side effects include pain on injection, postoperative nausea and vomiting, electroencephalic activation, adrenal suppression, and myoclonus (1,2).

Patients who have sustained open eye injuries are at risk of exacerbation of damage to the injured eye on induction of general anesthesia. Coughing, straining, hypoxia, and airway obstruction can rapidly increase intraocular pressure (IOP) (3–5). The combination of an open eye injury, a full stomach, and limited cardiovascular reserves produces a uniquely treacherous combination of circumstances for the anesthesiologist.

Case Report

A 38-yr-old, 90-kg man presented to the emergency room 1 hr after sustaining an injury to his left eye while repairing the brakes of his automobile.

He gave a 2-yr history of dyspnea on exertion, orthopnea, and nocturnal dyspnea and a 6-yr history of hypertension. He had been admitted to the hospital three times during the past 18 months for episodes of congestive heart failure. He had smoked for 20 yr and could tolerate walks of four blocks, limited by dyspnea. Eight months before presentation, cardiac catheterization revealed an ejection fraction of 25%, left atrial and ventricular enlargement, and hypokinesis with normal coronary arteries and valvular function. His dilated cardiomyopathy was ascribed to heavy and continuing alcohol use. He was poorly compliant with his regimen of furosemide, captopril, and diltiazem.

He had eaten a full meal 4 hr before the injury.

Physical examination revealed an obese male in pain. There was no jugular distension, peripheral edema, or respiratory distress. Ophthalmologic examination showed an open anterior chamber with a possible prolapse of irideal tissue; the posterior chamber was poorly seen. It could not be determined whether the eye was beyond repair.

There was old scarring and vascular prominence on chest x-ray, unchanged from 4 months previously. The electrocardiogram (ECG) demonstrated left ventricular hypertrophy and biatrial enlargement, without evidence of ischemia.

Consultation with the patient's ophthalmologist determined the immediate need for surgery and the need for general anesthesia. Preanesthetic management was discussed with the patient's cardiologist who felt that nothing more could be done immediately, and he was transferred to the surgical suite. Monitoring included ECG, intraarterial blood pressure, pulse oximetry, and mass spectrometry. An infusion of sodium nitroprusside was available for control of blood pressure during a modified rapid-sequence induction.

The patient was alert and awake with a blood pressure of 160/90 mm Hg and a pulse of 80 beats/min. Vecuronium 1 mg and fentanyl 0.2 mg were given 5 min before induction. Preoxygenation was followed by lidocaine 100 mg, vecuronium 9 mg, cricoid pressure, and etomidate. The etomidate injection was interrupted after 15 mg had been given by the onset of severe generalized myoclonus and hypertension. The blood pressure increased to 240/130 mmHg despite the rapid infusion of nitroprusside and was accompanied by arterial desaturation. Bleeding was seen coming from under the shield covering the injured eye. Thiopental 125 mg was given and the trachea was intubated. The myoclonus resolved after approximately 30 sec, and the blood pressure stabilized quickly with 1% isoflurane in oxygen. Examination of the eye revealed complete retinal detachment with some prolapse of vitreous. Since his preoperative examination had been limited, the ophthalmologic surgeon could not determine whether the eye had been further injured by the anesthetic induction. However, he decided that the eye was not viable and

---

Received from the Department of Anesthesiology, University of Texas Medical School, Houston, Texas. Accepted for publication March 31, 1989.

Address correspondence to Dr. Merin, Department of Anesthesiology, University of Texas Medical School at Houston, 6431 Fannin, MSB 5,020, Houston, TX 77030.

©1989 by the International Anesthesia Research Society

an enucleation was performed. During the 1-hr-long procedure, oxygen saturations slowly decreased to 90% with the appearance of rales and increased secretions. Furosemide and morphine were administered with resultant diuresis and improved arterial saturation. The patient awakened, the endotracheal tube was removed, and he was observed overnight in an intensive care unit. No further complications were noted and he was discharged 2 days later.

Discussion

This case provides a graphic illustration of the conflicting priorities in the planning and conduct of a high-risk anesthetic. Three areas were of the greatest concern: 1) a "full stomach" and the need for rapid control of the airway to prevent possible aspiration, 2) limited left ventricular performance and reserves, and 3) the presence of an open eye injury. The first problem, that of possible aspiration, has a low incidence but a high morbidity and mortality (6). The threat of left ventricular failure, although serious, is less life-threatening in the absence of ischemic heart disease (increased O_2 demand from increased filling pressures and decreased O_2 supply from decreased coronary perfusion). Open eye injuries demand an induction free of coughing or straining in order not to exacerbate the injury (4,5). In this case, with the real threat of aspiration of gastric contents, the combination of agents selected to minimize myocardial and ophthalmic stress was such that neither goal was met.

The use of etomidate for anesthesia is now almost 15 yrs old. Since its discovery by Janssen and clinical trials, it has proven to be a safe and effective alternative to thiopental in certain clinical settings (1). Its lack of effect on IOP is well documented (7,8), as are its minimal effects on cardiac performance in patients with preexisting heart disease (9–11).

The problem of involuntary muscle movements, or myoclonus, associated with etomidate, was recognized early in clinical trials (12). This reaction may be mild and transient, involving only a few axial muscle groups, or it may resemble generalized seizure activity (13). It has been related to pain on injection (14,15) and to the rate of injection (16,17). It is not clear whether this myoclonus represents seizure activity. Reports generally deny the association of etomidate with abnormal electroencephalographic activity (15,18), but one series of epileptic patients undergoing craniotomy had increased epileptiform activity during etomidate anesthesia (19). Prolonged myoclonus has been reported following total intravenous anesthesia with etomidate (20), yet early investigators found no clinical significance in what they described as only a transient aesthetic disturbance in an otherwise uneventful induction (1).

Table 1. Incidence of Myoclonus with Etomidate

Dose + Premed (mg/kg)	*n*	% Myoclonus	(% Severe)	Reference
0.3 + none	5	80		33
0.3 + none	9	78	(22)	22
0.2 + atropine 0.5 mg	14	64		31
0.3 + atropine 0.6 mg	50	64	(8)	21
0.3 + atropine 0.5 mg	20	65	(20)	15
0.3 + atropine 0.6 mg	50	22		34
0.3 + atropine 0.6 mg	200	30	(5)	17
0.3 + atropine 0.5 mg + fentanyl 0.1 mg	20	10		15
0.3 + atropine 0.6 mg + meperidine 50–100 mg	50	38	(0)	21
0.3 + papaveretum 0.3 mg/kg + promethazine 0.7 mg/kg	12	0		32
0.3 + atropine 0.5 mg ± fentanyl 0.1 mg ± diazepam 10 mg	30	60	(10)	16
0.3 + various	325	50	(12)	14
0.3 + various	100	25	(4)	35

An incidence of severe myoclonus (defined as resembling a generalized seizure) of 6–8% was reported by Holdcroft et al. (21) with an incidence of any myoclonus of 60% in patients given only atropine premedication. The observation that diazepam and/or fentanyl premedication diminish the incidence and severity of the effect has been made by others (14,15,17,21,22). Table 1 illustrates the incidence of reported myoclonus with etomidate.

The studies of IOP with etomidate anesthesia (in intact eyes) mention only that myoclonus, when seen, did not interfere with tonometry. It is not clear whether measurements were made during a myoclonic episode (8). Studies of etomidate also report a significant incidence of isolated eye movements (14). It seems unlikely that the extraocular and facial muscles would be spared in an episode of generalized myoclonus (13). Given the association of increased thoracic muscle tone (Valsalva's maneuver, straining) with increased IOP, generalized myoclonus would almost certainly greatly increase IOP. In fact, in patients anesthetized with thiopental and then given succinylcholine, further increases in IOP of up to 50 mm Hg are seen with the onset of electroconvulsion (23).

The choice of muscle relaxant in the patient with an open eye injury remains controversial (4,5). Early reports of increased IOP with succinylcholine (23–25) have led to increased reliance on nondepolarizing drugs (4,5,26). The introduction of more rapid-acting neuromuscular blockers has improved, but not completely alleviated the problem of a rapid-sequence induction in the open globe patient. Vecuronium does not affect IOP in the anesthetized patient (27), and priming techniques have been documented to reduce the time to complete relaxation to approximately 60 sec with vecuronium or pancuronium (28,29). As well, very high dose vecuronium or atracurium may provide satisfactory intubating conditions in approximately 60 sec (30). However, Libonati et al. (3) suggest that the transient increase in IOP induced by succinylcholine may not be clinically significant.

The use of etomidate in rapid-sequence induction of anesthesia has not been well studied. Comparisons of techniques for rapid-sequence induction have all used thiopental. Myoclonus would seem to be an unpredictable complication of etomidate use and is obviously hazardous in the patient with an open eye. It then seems prudent, when rapid relaxation is needed for airway control, to use a relaxant which would minimize the time to complete flaccidity. The small, transient increase in IOP with succinylcholine is insignificant in comparison to the dramatic response in myoclonus (3). So, when it is deemed necessary to utilize the cardiovascular stability provided by etomidate induction in the patient with an open eye, etomidate should be combined with succinylcholine, with or without a "defasciculating" dose of nondepolarizing relaxant. The use of narcotic and/or benzodiazepine may reduce the incidence of myoclonus. We suggest that the use of etomidate in the patient with an open globe without the rapid muscle relaxation produced by succinylcholine invites the possibility of loss of ocular contents.

There is a need for further study and clarification of the relationship of myoclonus to IOP, as well as defining more precisely the dynamics of rapid-sequence inductions utilizing etomidate.

References

1. Giese JL, Stanley TH. Etomidate: a new intravenous anesthetic induction agent. Pharmacotherapy 1983;3:251–8.
2. Wagner RL, White PF, Kar PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 1984;310:1415–21.
3. Libonati MM, Leahy JJ, Ellison N. The use of succinylcholine in open eye surgery. Anesthesiology 1985;62:637–40.
4. Murphy DF. Anesthesia and intraocular pressure. Anesth Analg 1985;64:520–30.
5. Cunningham AJ, Barry P. Intraocular pressure—physiology and implications for anaesthetic management. Can Anaesth Soc J 1986;33:195–208.
6. Gibbs CP, Modell JH. Aspiration pneumonitis. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1986:202.
7. Thomson MF, Brock-Utne JG, Bean P, Welsh N, Downing JW. Anaesthesia and intra-ocular pressure: a comparison of total intravenous anaesthesia using etomidate with conventional inhalation anaesthesia. Anaesthesia 1982;37:758–61.
8. Calla S, Gupta A, Sen N, Garg IP. Comparison of the effects of etomidate and thiopentone on intraocular pressure. Br J Anaesth 1987;59:437–9.
9. Colvin MP, Savege TM, Newland PE, Weaver EJM, Waters AF, Brookes JM, Inniss R. Cardiorespiratory changes following induction of anaesthesia with etomidate in patients with cardiac disease. Br J Anaesth 1979;51:551–6.
10. Gooding JM, Weng J-T, Smith RA, Berninger GT, Kirby RR. Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease. Anesth Analg 1979;58:40–4.
11. Reneman RS, Janssen PA. The experimental pharmacology of etomidate, a new potent, short-acting intravenous hypnotic. In: Doenicke A, ed. Etomidate, an intravenous hypnotic agent. Berlin: Springer-Verlag, 1977:1–5.
12. Doenicke A: Etomidate, a new hypnotic agent for intravenous application. In: Doenicke A, ed. Etomidate, an intravenous hypnotic agent. Berlin: Springer-Verlag. 1977:25–30.
13. Aigner BR, Mulder DW. Myoclonus: clinical significance and an approach to classification. Arch Neurol 1960;2:600–15.
14. Schuermans V, Dom J, Dony J, Scheijgrond H, Brugmans J. Multinational evaluation of etomidate for anesthesia induction. Anaesthesist 1978;27:52–9.
15. Ghoneim MM, Yamada T. Etomidate: a clinical and electroencephalographic comparison with thiopental. Anesth Analg 1977;56:479–85.
16. Fragen RJ, Caldwell N, Brunner EA. Clinical use of etomidate for anesthesia induction: a preliminary report. Anesth Analg 1976;55:730–3.
17. Lees NW, Hendry JGB. Etomidate in urological outpatient anaesthesia. Anaesthesia 1977;32:592–602.
18. Kugler J, Doenicke A, Lab M. The EEG after etomidate. In: Doenicke A, ed. Etomidate, an intravenous hypnotic agent. Berlin: Springer-Verlag, 1977:31–48.
19. Ebrahim ZY, DeBoer GE, Luders H, Hahn JF, Lesser RP. Effect of etomidate on the electroencephalogram of patients with epilepsy. Anesth Analg 1986;65:1004–6.
20. Laughlin TP, Newberg LA. Prolonged myoclonus after etomidate anesthesia. Anesth Analg 1985;64:30–2.
21. Holdcroft A, Morgan M, Whitwam JG, Lumley J. Effect of dose and premedication on induction complications with etomidate. Br J Anaesth 1976;48:199–205.
22. Doenicke A, Kugler J, Penzel G, Laub M, Kalmar K, Killian I, Bezecny H. Hirnfunktion und Toleranzbreite nach Etomidate, einem neuen barbituratfreinen i.v. applizierbaren Hypnoticum. Anaesthesist 1973;22:357–66.
23. Lincoff HA, Ellis CH, DeVoe AG, DeBeer EJ, Impastato DJ, Berg S, Orkin L, Magda H. The effect of succinylcholine on intraocular pressure. Am J Ophthalmol 1955;40:501–10.
24. Taylor TH, Mulcahy M, Nightingale DA. Suxamethonium chloride in intraocular surgery. Br J Anaesth 1968;40:113–8.
25. Hofman H, Holzer H. Die Wirkung von Muskelrelaxantien auf den intraocularen Druck. Klin Monatsbl Augenheilkd 1953; 123:1–16.
26. Cook JH. The effect of suxamethonium on intraocular pressure. Anaesthesia 1981;36:359–65.
27. Sia RL, Rashkovsky OM. Org NC45 and intraocular pressure during anaesthesia. Acta Anaesthesiol Scand 1981;25:219–21.
28. Schwarz S, Ilias W, Lackner F, Mayrhofer O, Foldes FF. Rapid tracheal intubation with vecuronium: the priming principle. Anesthesiology 1985;62:388–91.
29. Mehta MP, Choi WW, Geris SD, Sokoll MD, Adolphson AJ. Facilitation of rapid endotracheal intubations with divided

doses of nondepolarizing neuromuscular blocking drugs. Anesthesiology 1985;62:392–5.

30. Lennon RL, Olson RA, Gronert GA. Atracurium or vecuronium for rapid sequence endotracheal intubation. Anesthesiology 1986;64:510–3.

31. Rifat K, Gamulin Z, Gemperle M. Etomidate: effets cardiovasculaires du nouvel agent anesthesique intraveineux. Can Anaesth Soc J 1976;23:492–504.

32. Colvin MP, Savege TM, Newland PE, Weaver EJM, Waters AF, Brookes JM, Inniss R. Cardiorespiratory changes following induction of anaesthesia with etomidate in patients with cardiac disease. Br J Anaesth 1979;51:551–6.

33. Kettler D, Sonntag H, Donath U, Regensburger D, Schenk HD. Hämodynamik, Myokardmechanik, Sauerstoffbedarf und Sauerstoffversorgung des menschlichen Herzens unter Narkoseeinleitung mit Etomidate. Anaesthesist 1974;23:116–21.

34. Miller BM, Hendry JGB, Lees NW. Etomidate and methohexitone. Anaesthesia 1978;33:450–3.

35. Morgan M, Lumley J, Whitwam JG. Etomidate: a new water-soluble non-barbiturate intravenous induction agent. Lancet 1975;1:955–6.

Fifty-Two Years Ago in
Anesthesia & Analgesia

F. H. McMechan, L. McMechan: Elmer Isaac McKesson, MD, Anesthetist: His Life and Work. 1937;16:1–6.

Elmer Isaac McKesson, born in 1881 in a small rural village in Indiana, received his medical degree from Rush Medical College in Chicago in 1906. During his internship in 1907 at the Toledo Hospital in Toledo, Ohio, he decided to devote his career to anesthesia at a time when anesthesia was, at best, at its prepubertal stage of development in the United States—and, for the most part, throughout the rest of the world. By the time he died in 1935, he had become an internationally recognized leader in and contributor to the development of anesthesia.

His contributions were made in three areas. First, McKesson was a skilled inventor and producer of anesthesia equipment. Almost single-handedly he revolutionized equipment used in anesthesia including basic things such as reliable pressure-reducing valves and flow meters to systems capable of accurately delivering different concentrations of nitrous oxide and oxygen despite rapidly and erratically changing flow rates needed to meet inflow demands on the delivery system by spontaneously breathing patients. He was an inventor. He was also a skilled mechanic and engineer, so skilled that he could commercially produce the equipment he invented. And he did not go broke doing so.

Second, by concentrating his attention almost exclusively on nitrous oxide, he became world famous for his exploitation to the fullest of this gas. For him nitrous oxide-oxygen was the alpha and omega of general anesthetics. In his hands, nitrous oxide could be used as a complete anesthetic. McKesson's clinical skill and his mastery of the art of anesthesia, combined with his knowledge of respiratory physiology and the efficiency and practicality of the anesthesia machines he made and used, made him a pioneer in the establishment of nitrous oxide as a major component of general anesthesia yesterday and today. Not all anesthetists of the time were as willing (or able) to use nothing but nitrous oxide-oxygen for intra-abdominal as well as all other types of operations in all sorts and conditions of patients. But McKesson had physiologic reasons to support what he preached, even in something as outrageous as primary and secondary saturation with nitrous oxide. This consisted basically of inducing anesthesia in patients by substituting the room air they were breathing with 100% nitrous oxide (no oxygen) and then, just before disaster occurred, giving them 80% nitrous oxide in oxygen, or perhaps a breath or two of 100% oxygen before starting the 80% nitrous in oxygen. That his patients survived this almost instantaneous induction of anesthesia was because of timing and, above all, because, of course, alveolar oxygen tension increased when patients breathing room air started breathing 100% nitrous oxide for the same reasons that alveolar oxygen tension decreases at the end of a nitrous oxide anesthetic when patients go from breathing 80% nitrous to breathing room air, i.e., diffusion hypoxia.

Finally, McKesson was deeply involved in the establishment of a number of organizations and institutions that were important then and are still important today, whether in an unchanged form or as descendants of previous organizations. He was either a charter member or a founder, or both, of societies such as the New York Society of Anesthetists, the American Association of Anesthetists, and the International Anesthesia Research Society. The importance of these societies in the organization of modern anesthesia need not be repeated, having been previously reviewed in this series of Historical Notes, but suffice it to say that McKesson's claim to fame lies in more than his development of anesthesia equipment and his use of nitrous oxide.

The authors, Dr. McMechan and his wife, were just as important as McKesson. They will be afforded a separate Historical Note in the future.

Letters to the Editor

"Sciatic Radicular Pain" or Piriformis Muscle Syndrome?

To the Editor:

Xavier et al. (1) recently published a report about the relief of "sciatic radicular pain," and we commend the authors for taking the initiative to publish these five cases in which they have demonstrated that sciatica can be treated by sciatic nerve block. As we understand, sciatica is a symptom and not a disease, and it is seldom caused by primary neuritis.

The authors presented an excellent description of the cases, and wrote a thorough discussion of all the possible mechanisms of pain relief. They also gave well deserved consideration to various etiologic factors for sciatica except one (i.e., piriformis muscle syndrome), and because of that, their conclusion was not quite accurate. In our pain clinic, we have observed that many patients with low back pain of either nonsurgical etiology or postlaminectomy syndrome, with or without electromyographic (EMG) findings positive for "radiculopathy," have piriformis muscle syndrome.

Yeoman (2) was first to refer to the piriformis muscle syndrome and its relationship with sciatica. The piriformis muscle syndrome is one of the differential diagnoses to consider in patients with low back pain, and the physical examination of these patients is very similar to those for back pain of different etiologies (3). Its relationship with the postlaminectomy pain syndrome and mechanisms of sciatica have been described (4). To diagnose piriformis muscle syndrome, one has to look for it by deep palpation of the piriformis muscles. Pain relief in these patients after the direct infiltration of piriformis muscle with a local anesthetic is dramatic. Because of the anatomic relationship of the piriformis muscle and sciatic nerve, there is a 20% chance of at least partial sciatic nerve block (5) when the piriformis muscle is infiltrated with local anesthetic solutions.

Xavier et al. (1) used an anterior approach for sciatic nerve block, and obtained the pain relief either by direct injection of the muscle or retrograde block (6) of S_1-S_2, thus relieving sciatic nerve compression.

Abram's accompanying editorial (7) is an excellent treatise on the neurophysiology of the pain mechanisms. However, he failed to clearly explain the pain relief secondary to sciatic nerve block in patients such as those reported by Xavier et al. (1). He admitted even more difficulty explaining the duration of the pain relief based on available reported findings. The onset of pain relief in the patients of Xavier et al. (1) was 20 min to 1 hr, and duration was 2 days to 2 weeks. Piriformis muscle injection will produce variable pain relief. Duration of pain relief reported by Xavier et al. (1) was very similar to that reported by Bonica (8).

Although it is important, as after completion of any scientific investigation, to analyze all observations and draw conclusions for future use, one should exhaust all probable and even possible explanations (based on prior studies) before invoking a new theory or mechanism for pain relief, especially those based on such a small number of cases. This could mislead practitioners involved in pain management to try a new treatment without the complete understanding of its indications, limitations, and complications. As Abram (7) pointed out, "there is a low but real risk of nerve damage with peripheral nerve block, and repeated local anesthetic blocks of sciatic nerves have been reported to cause myositis, myelin vacuolization of the nerve, and impaired nerve function in animals."

Because of positive EMG findings in four of the five patients reported by Xavier et al. (1), the authors concluded that the entire etiology of pain syndromes in those patients was caused by "radiculopathy." In my opinion, they have described an anterior approach for treatment of piriformis muscle syndrome.

Zia Durrani, MD
Pain Clinic
Department of Anesthesiology and Pain Clinic
The University of Illinois at Chicago
Suite 3200 West
1740 West Taylor Street
Chicago, IL 60612

References

1. Xavier AV, McDanal J, Kissin I. Relief of sciatic radicular pain by sciatic nerve block. Anesth Analg 1988;67:1177–80.
2. Yeoman W. The relation of arthritis of the sacroiliac joint to sciatica. Lancet 1928;2:1119–22.
3. Kirkaloy-Willis WH, Hill RJ. A more precise diagnosis of low back pain. Spine 1979;4:102–9.
4. Mizuguchi T. Division of the pyriformis muscle for the treatment of sciatica. Arch Surg 1976;111:719–22.
5. Pecina M. Contribution to the etiological explanation of the pyriformis syndrome. Acta Anat (Basel) 1979;105:181–7.
6. Moor DC, Hain RF, Ward A, Bridenbaugh LD. Importance of perineural spaces in nerve blocking. JAMA 1954;13:1050–3.
7. Abram SE. Pain mechanism in lumbar radiculopathy (editorial). Anesth Analg 1988;67:1135–7.
8. Bonica JJ. The management of pain. Philadelphia: Lea & Febiger, 1954: 910.

©1989 by the International Anesthesia Research Society

Pseudosciatica

To the Editor:

I read with interest the article by Xavier et al. (1), describing the phenomenon of distal nerve block affecting centrally mediated pain. I propose an alternate explanation. In "pseudosciatica," the sciatic nerve is compressed by a contracted piriformis muscle against the obturator internus and the sharp edge of the greater sciatic notch (2), or it is compressed as it courses through the body of the muscle itself (3), in both instances producing sciatic pain radiating down the leg to the foot. Motor weakness with a limp on the affected side has been reported (4). The fifth lumbar vertebra, sacrum, and sacroiliac joint have been regarded as comprising a structural and functional unit (5). Injury to any of these structures commonly results in a "piriformis syndrome" with sciatic-like symptoms.

For example, a 30-year-old white male presented with a 10-week history of low bck pain radiating to his leg and foot, associated with numbness of his proximal leg and a significant foot drop. Examination revealed diminished pin prick sensibility over the L2-L4 dermatomes and a positive straight leg raising (SLR) sign at 30° of flexion. In this test, the sciatic nerve is stretched during supine hip flexion by elevating a straightened leg. The hip is slightly adducted, held in neutral position, and the foot is held at 90°. A positive test produces pain that radiates to the foot. The patient also had tenderness to palpation over both his sacroiliac (SI) joint and his piriformis muscle, where a significant nodule was felt. The piriformis muscle was injected via a posterior approach with a total of 5 ml of 1% lidocaine, using the technique of Travell and Simons (6). Immediate improvement in pin prick sensibility was associated with decreased pain. No evidence of sciatic nerve block was present on subsequent reexamination. His limp resolved. A residual SLR sign at approximately 75° prompted injection of the SI joint with 0.5% bupivacaine and methylprednisolone acetate. A series of injections of the SI joint with bupivicaine and methylprednisolone, and the piriformis muscle with lidocaine, resulted in complete resolution of all symptoms and full resolution of his limp.

I propose that the patients described by Xavier et al. (1) had piriformis syndrome, probably secondary to lumbar joint disease. The volumes of local anesthetic used could have easily produced an incidental piriformis block. Radicular pain can only be differentiated from pseudosciatica by electromyographic demonstration of nerve involvement above and below the piriformis muscle (i.e., involvement of the gluteal and tensor fascia lata muscles, as well as distal innervation).

It is conceivable that a significant proportion of patients with sciatic pain are actually experiencing piriformis syndrome associated with abnormalities in facet joints, sacroiliac joints, etc. This might explain the high failure rates for current treatment modalities that only address peridural processes.

Gary Arthur Ogin, MD
University of Colorado
Department of Anesthesiology
Denver, CO 80220

References

1. Xavier AV, McDanal J, Kissin I. Relief of sciatic radicular pain by sciatic nerve block. Anesth Anal 1988;67:1177–80.
2. Borenstein DG, Wiesel SW. Low back pain. Philadelphia: WB Saunders, 1989:390–2.
3. Mennell JB. The science and art of joint manipulation. London: Churchill Livingstone, 1952.
4. Pace JB, Nagle D. Piriformis syndrome. West J Med, 1976;124:435.
5. Grieve G. Common vertebral joint problems. London: Churchill Livingstone, 1981:295–6.
6. Travell J, Simons D. Myofascial pain and dysfuction. Baltimore: Williams and Wilkins, 1983:82–5.

Sciatica and the Cerebrospinal Fluid

To the Editor:

In relation to the report on nerve block for the relief of sciatic radicular pain (1) and the editorial commentary thereto (2), it is sobering to know that sciatica has been a common affliction of bipedal man as far back as recorded history. Indeed, the prevalence of sciatica in Naples around 1764 coincidentally resulted in the first comprehensive description of the cerebrospinal (CSF) circulation (3). According to Viets (4), Dominico Felice Antonio Çotugno, anatomist and physician, encountered a host of cases of sciatica soon after beginning service at the Ospedali degli Incurabili ("Sciatica was a common disease, filling the wards and the churches with its victims"). Subsequently, in his celebrated treatise, *De Ischiade Nervosa Commentarius* (5), Cotugno listed the causes of sciatica as previously categorized by Hippocrates (Abram's editorial [2] covers some of the same ground). However, Cotugno focused on a true nervous form, in which the disease is localized to the sciatic nerve itself. He ascribed this condition to acrid and irritating matter in CSF that passes into the cavities as well as the cellular sheath around it. Therefore, his studies on the circulation of CSF were designed to strengthen this hypothesis.

Parenthetically, demurrers not withstanding, it is highly probable that sciatic nerve block, performed with 15 ml of anesthetic solution, injected via the anterior approach with or without paresthesias, or intraneural placement, into the nerve vascular sheath of that great nerve results in extensive central spread of the anesthetic. Where is the additional diffusion site of the block—epidural or subarachnoid space?

Leroy D. Vandam, MD
Department of Anesthesia
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115

References

1. Xavier AV, McDanal J, Kissin I. Relief of sciatic radicular pain by sciatic nerve block. Anesth Analg 1988;67:1177–80.

2. Abram SE. Pain mechanisms in lumbar radiculopathy (editorial). Anesth Analg 1988;67:1135–7.
3. Vandam LD. Back pain and sciatica. Letter to the editor. N Engl J Med 1988;319:312–3.
4. Viets HR. Dominico Cotugno: his description of the cerebrospinal fluid. Bull Inst Hist Med 1935;3:701–20.
5. Cotugno D. De ischiade nervosa commentarius. Neapoli: Fratres Simionis, 1764.

Blockade of Sciatic Nerve Branches Relieves Sciatic Radicular Pain

In Response:

We thank Drs. Durrani, Ogin, and Vandam for responding to our recently published report (1). Their explanations for the phenomenon of sciatic radicular pain relief by sciatic nerve block are based on the proximity of the site of blockade to the piriformis muscle (incidental piriformis block in piriformis syndrome) or the injured root (retrograde block). However, we have found that blockade of the branches of the sciatic nerve at a significant distance from both the piriformis muscle and the injured root also produces relief of the pain in sciatica. Table 1 presents five cases of lumbar radiculopathy (confirmed by the EMG study) in which we examined the effect of blockade of the sciatic nerve branches. In two patients, the tibial nerve was blocked at the ankle, and in three other patients, the tibial and common peroneal nerves were blocked in the popliteal fossa. With the tibial nerve block at the ankle, 7 ml of 1% lidocaine solution was used, whereas 30 ml of 0.5% bupivacaine was administered for the tibial and common peroneal block in the popliteal fossa. Change in sensitivity to pinprick was used as an indicator of the blockade. The effect of the block on pain intensity was assessed with the use of the visual analog scale in the low back and in the distribution of the sciatic nerve at three different levels: thigh, calf, and foot. *One would not expect the block (distal to the site of the root injury) to abolish the perception of pain resulting from orthodromic transmission of ectopic impulses arising in the injured root. However, like it was with sciatic nerve block (1), blockade of the sciatic nerve branches resulted in complete pain relief below the site of injection.* It is highly unlikely that the local anesthetic could produce the effect by reaching the injured root through proximal spread of the drug along the tibial (peroneal) and the sciatic nerves from the ankle level. A direct effect of the anesthetic on the piriformis muscle is also excluded.

Not less interesting was the finding of pain relief above the level of blockade. In all three cases with the blockade at the knee level, the pain disappeared not only below the knee, but also in the thigh area. With blockade at the ankle level, in one case, there was a complete pain relief in the sciatic nerve distribution in the foot, the calf, and the thigh. In the other case, the pain was completely relieved in the foot (from 6 to 0), decreased in intensity in the calf (from 6 to 2), and was not changed in the thigh. In all five cases there was no significant change in the low back pain. The observation that block-induced pain relief in one area results in pain relief in the adjacent nonblocked areas suggests central nervous system involvement in the mech-

Table 1. Effect of Neural Blockade on Pain in Lumbar Radiculopathy

Patient no.	Gender/age	Diagnosis	Block location	Pain intensity (0 to 10 scale) Before block	After block
1	F 57	Left S_1 radiculopathy	Tibial nerve at ankle	LB 8	LB 8
				T 6	T 6
				C 6	C 2
				Ft 6	Ft* 0
2	F 57	Right L_5 radiculopathy	Tibial nerve at ankle	LB 10	LB 10
				T 10	T 0
				C 10	C 0
				Ft 10	Ft* 0
3	M 45	Right S_1–S_2 radiculopathy	Tibial and common peroneal nerves in popliteal fossa	LB 8	LB 8
				T 5	T 0
				C 7	C* 0
				Ft 8	Ft* 0
4	F 39	Left L_5 radiculopathy	Tibial and common peroneal nerves in popliteal fossa	LB 7	LB 8
				T 7	T 0
				C 7	C* 0
				Ft 7	Ft* 0
5	F 38	Right L_5 radiculopathy	Tibial and common peroneal nerves in popliteal fossa	LB 7	LB 6
				T 7	T 0
				C 3	C* 0
				Ft 3	Ft* 0

*Regions with blocked nervous pathways. C = calf; F = female; Ft = foot; LB = low back; M = male; T = thigh.

anism of the therapeutic effect of sciatic nerve block in radicular pain.

We hypothesize that the beneficial effect of sciatic block in chronic radicular pain depends on the two following pathophysiologic mechanisms underlying sciatica. First, sciatica depends on impulses originating peripheral to the injured root, most likely as a result of antidromic activation of nociceptors (2). Neural blockade distal to the injured root provides pain relief by abolishing antidromic impulsation and antidromically induced input from peripheral nociceptors. Second, antidromically induced nociceptive input leads to sensitization of the receptive cells in the central pain projection system that maintain chronic sciatic pain. Blockade of the ongoing afferent impulses results in a return of the central nociceptive neurons to a normal level of sensitivity, leading to pain relief that outlasts the duration of the neural blockade.

We would like to make the following comments on piriformis syndrome. This syndrome is uncommon. In Pace and Nagle's series (1) of 750 cases from a specialized back clinic, only 45 patients with piriformis syndrome were recorded, an incidence of 6%. Piriformis syndrome often occurs secondary to root irritation in lumbar disc disease (4). The piriformis muscle relationship to the sciatic nerve is such that injection of a local anesthetic into the muscle can result in blockade of the sciatic nerve. The latter two facts suggest that pain relief after injection into the piriformis muscle may result from incidental sciatic nerve block.

Igor Kissin, MD, PhD
Anne V. Xavier, MD
Judy McDanal, MD
Department of Anesthesiology
University of Alabama at Birmingham Medical Center
Birmingham, AL 35294

References

1. Xavier AV, McDanal J, Kissin I. Relief of sciatic radicular pain by sciatic nerve block. Anesth Analg 1988;67:1177–80.
2. Xavier AV, McDanal J, Kissin I. Mechanism of pain in sciatica. Neurology 1989;39:601–2.
3. Pace JB, Nagle D. Piriform syndrome. West J Med 1976;124:435–9.
4. Finneson BE. Low back pain, 2nd ed. Philadelphia: Lippincott, 1980:536.

"Statistical Power" and Interpretation of Small Studies: Does Atracurium Pretreatment Reduce the Incidence of Succinylcholine Fasciculations?

To the Editor:

We read with some statistical concern the original article (1) and subsequent correspondence (2) relating to the study of Sosis et al., which compared the use of atracurium and d-tubocurarine in the prevention of succinylcholine-induced fasciculation and myalgia. Our concern relates not to the statistical methods used (the primary responses were binary [fasciculation y/n, myalgia y/n], and, in view of the small numbers, there was little option but to use Fisher's exact test) but rather to the failure of the original authors and the subsequent correspondents to recognize the difficulty of making inferences from small studies such as this.

The problem arises from the lack of "power" of small analyses—"power" being the ability of a statistical analysis to detect a *true* effect if it *really* exists. It is therefore of interest to estimate the approximate "power" of the Sosis analysis: if one considers the comparison between atracurium and normal saline in the prevention of fasciculation (the comparison of prime interest to the correspondents), then, given that the observed proportion of fasciculating cases in the normal saline group was around 80%, one can approximately calculate the power of the analysis to detect a *true* halving of the fasciculating rate to 40% in the atracurium group. Using standard formulas (3) and accepting $P < 0.05$ as the defined level of statistical significance, it is possible to estimate that the Sosis study had only a 64% chance of detecting even such a large effect as this, and, although this may appear reasonable, it should be recognized that the tossing of a coin carries an implicit power of 50%. Thus, even if atracurium *did* beneficially influence fasciculation it should come as no surprise that this study was unable to demonstrate the benefit.

Like the first correspondents, we too have reanalyzed the Sosis data. However, contrary to their results, we find that a one-tailed Fisher's test (calculated both by hand and by computer) provides a P value of 0.089 (not 0.043) for the difference of interest, and, in any case, it is more appropriate to use a *two-tailed* test in this instance. Although this result is not of a magnitude sufficient to permit outright rejection of the null hypothesis (that no true difference exists between atracurium and normal saline in the control of succinylcholine fasciculation), we do not draw the conclusion that atracurium *does not* reduce fasciculation but rather that this study is of an inadequate size to reliably detect such an effect—a distinction that has important practical implications.

Paul Burton, BSc, MRCP
Jennifer Kurinczuk, BSc, MB, ChB
Department of Community Health
University of Leicester
Leicester LE2 7LX
United Kingdom

Eric De Melo, MB, ChB
Department of Anaesthetics
Leicester Royal Infirmary
Leicester LE1 5WW
United Kingdom

References

1. Sosis M, Broad T, Larijani GE, Marr AT. Comparison of atracurium and d-tubocurarine for prevention of succinylcholine myalgia. Anesth Analg 1987;66:657–9.
2. Herlich A, Eisenkraft JB, Hubbard M. Atracurium pretreatment for prevention of succinylcholine fasciculations. Anesth Analg 1988;67:419.
3. Armitage P. Statistical methods in medical research. Oxford and Edinburgh: Blackwell Scientific Publications, 1971:184–8.

Venous Air Embolism during Hip Arthrography

To the Editor:

A 6-kg 3-month-old female with chronic left hip subluxation was scheduled for an examination under anesthesia, a double contrast left hip arthrogram, and placement of a hip spica cast. The child was delivered at 38 weeks' gestation by cesarean section without complications and had a normal perinatal course. Physical examination before surgery was unremarkable.

Anesthesia was induced by mask with halothane/nitrous oxide/oxygen and a 22-gauge intravenous cannula was placed in a left wrist vein. Atropine (0.12 mg) and atracurium (3 mg) were given intravenously, followed by intubation with a 3.5-mm uncuffed tube. Anesthesia was maintained with 35% O_2/65% N_2O, and 0.5 to 1% halothane. Monitors included an electrocardiogram (ECG), blood pressure cuff, precordial stethoscope, pulse oximeter, and a rectal temperature probe. The ECG showed a sinus rhythm at 160 beats/min. Arterial oxygen saturation was 99%, and blood pressure was 88/50 mm Hg after induction and intubation.

A left hip arthrogram was performed by inserting a 22-gauge needle, using an anterolateral approach. Two 5-ml injections of air were used to confirm correct needle placement. Two to 3 min after the second injection, a millwheel murmur was heard over the precordium, followed by a precipitous decrease in oxygen saturation (to 85%), blood pressure (to 65/30 mm Hg), and heart rate (to 70 beats/min). The ECG showed an atrioventricular 2:1 conduction block in lead II. The patient's lungs were immediately ventilated with 100% oxygen, the halothane was discontinued, and 0.1 mg of atropine was given intravenously. The atropine was repeated after 30 s. Approximately 2 min later, blood pressure increased to 100/65 mm Hg, the heart rate returned to 160 beats/min in sinus rhythm, and the oxygen saturation returned to 99%. At the same time, the murmur resolved. The remainder of the anesthetic course was uneventful. The child was extubated in the operating room, fully alert and grossly neurologically intact. The postanesthetic course was unremarkable, and the child was discharged from the hospital the next day.

This case describes the danger associated with such a supposedly routine procedure. Fortunately in our case, a disastrous outcome was avoided. We would like to reemphasize that early detection of a venous air embolism does not preclude the absence of a major morbidity or mortality, which obviously is determined by a myriad of variables not controllable by the anesthesiologist. More importantly, we need to continue to educate orthopedic surgeons about the inherent danger of injecting air into a joint (1,2), and encourage the use of more soluble agents such as CO_2, N_2O, or even H_2O as contrast mediums.

Richard G. Hetherington, DO, and
Patrick M. McQuillan, MD
Department of Anesthesiology
Naval Hospital
Portsmouth, VA 23708-5800

References

1. McCauley GK, Wunderlich BK, Zimbler MD. Air embolism as a complication of hip arthrography. Skel Radiol 1981;6:11–3.
2. Saha AK. Air embolism during anaesthesia for arthography in a child. Anaesthesia 1976;31:1231–3.

Cimetidine in Anaphylactic Shock Refractory to Standard Therapy

To the Editor:

Anaphylaxis, the most severe form of an allergic reaction, can occur after the administration of many drugs in the operating room. Recently, H_2 blockers have been reported to be effective in the treatment of acute allergic reactions (1–3). We now report a case of anaphylactic shock due to a cephalosporin that improved dramatically with the administration of cimetidine.

A 48-year-old, 65-kg female was admitted to the hospital for repair of a perilymphatic fistula in the left ear. Prior medical and anesthetic history was unremarkable. There was no history of drug allergies. Physical examination was unremarkable.

The patient was brought to the operating room following oral premedication with 10 mg of diazepam. Anesthesia was induced with 250 mg thiopental and intubation was facilitated by 6 mg vecuronium. Anesthesia was maintained with 60% nitrous oxide, 40% oxygen, and 1% isoflurane.

Before the incision was made and while vital signs were stable (blood pressure 120/80 torr; heart rate 80 bpm), the surgeon requested that we administer one gram of cefuroxime (a broad spectrum cephalosporin) IV. The agent was diluted in 100 mL of normal saline and an IV infusion started. When the surgeons were ready to begin the operation and when approximately 50 mL of the antibiotic solution had been administered, the blood pressure suddenly decreased to 40/20 torr, and the heart rate increased to 150 bpm. At the same time, the patient developed a severe diffuse erythema.

Administration of the antibiotic was immediately stopped, anesthetic agents were discontinued, and 100% oxygen was administered. Rapid administration of IV fluids was begun, and 15 mg mephentermine along with 0.5 mg epinephrine were administered IV. Blood pressure and heart rate remained unchanged, and an additional 0.5 mg epinephrine was administered IV, along with 50 mg diphenhydramine and 250 mg hydrocortisone. After a few min without response, an epinephrine 1:1000 infusion was started at a rate of 4 μg/min. The blood pressure increased to 70/40 torr, but the heart rate remained 140 bpm. By this time 2000 mL of crystalloids had been administered. A

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy or the Department of Defense.

decision was made then to administer 300 mg of cimetidine IV. This was given over 10 min, during which time the blood pressure returned to 110/70 torr, and the heart rate stabilized at 90 bpm. Epinephrine was discontinued. No wheezing or bronchospasm occurred during the event. The erythema though, persisted for 24 hours. The patient was discharged from the hospital five days later without further problems.

Cimetidine, an H_2 receptor antagonist, has been widely used in the treatment of gastric and duodenal ulcers since 1971 (4–7). Many authors have reported the benefits of H_2 receptor blockers for chronic idiopathic urticaria (5–7). The advantages of the combination of H_1 and H_2 receptor blockers have also been reported (8–10).

We could find no report on use of H_2 blockers in the treatment of anaphylactic shock occurring intraoperatively. Exactly how or why H_2 blockers function in anaphylaxis is not known. It is now widely accepted, however, that human cutaneous vessels contain both H_1 and H_2 receptors and that histamine effects on these receptors is considered the mechanism involved (9,11,12). Recently, Plaut described several possible effects of H_2 antihistamines on immediate hypersensitivity reactions (13). He believes that H_2 blockers may act synergistically with H_1 antihistamines on vascular receptors, block H_2 antiinflammatory receptors, inhibit histamine metabolism, promote catecholamine release, induce histidine decarboxylase, and change H_2 receptor turnover rate (13).

Several questions remain unanswered in our case. What really made the patient get better? Was it the H_2 blocker itself? Was it the H_2 blocker combined with the other treatments? Would the patient have recovered without the H_2 blocker? We do not have answers to these questions, although the addition of cimetidine appeared to restore a normal blood pressure and allow discontinuation of pharmacologic pressure support.

In summary, we describe a case of anaphylaxis refractory to standard therapy in which the use of an H_2 blocker restored hemodynamic stability. Further studies are warranted to explore the use of cimetidine in the treatment of anaphylaxis.

Hernando De Soto, MD
Paul Turk, MD
Medical College of Georgia
Augusta, GA 30912-2277

References

1. Mayumi H, Kimura S, Ananso M, et al. Intravenous cimetidine as an effective treatment for systemic anaphylaxis and acute allergic skin reactions. Ann Allergy 1987;58:447–50.
2. Rusli M. Cimetidine treatment of recalcitrant acute allergic urticaria. Ann Emerg Med 1986;15:1363–5.
3. Gerlock GA. Cimetidine: a useful drug for treatment of anaphylaxis. J Am Assoc Nurse Anesth 1983;51:608–10.
4. Black JW, Duncan WAM, Durant CJ, et al. Definition and antagonism of histamine H-2 receptors. Nature 1972;236:385–90.
5. Commens CS, Greaves MW. Cimetidine in chronic idiopathic urticaria: a randomized double blind study. Br J Dermatol 1978;99:675–9.
6. Farman J, Grant JA, Guernsey BG, et al. Successful treatment of chronic idiopathic urticaria and angioedema with cimetidine alone. J Allergy Clin Immunol 1984;73:842–5.
7. Kaiser HB, Weisberg SC, Morris RJ. Cimetidine in chronic urticaria. Lancet 1980;260:July26.
8. Monroe EW, Cohen SH, Kalbfleisch J, et al. Combined H-1 and H-2 antihistamine therapy in chronic urticaria. Arch Dermatol 1981; 117:404–7.
9. Harvey RP, Wegs J, Schocket AL. A controlled trial of therapy in chronic urticaria. J Allergy Clin Immunol 1981;68:262–6.
10. Philbin DM, Moss J, Akins CW, et al. The use of H-1 and H-2 histamine antagonists with morphine anesthesia: a double-blind study. Anesthesiology 1981;55:292–6.
11. Davies MG, Marks R, Horton RJ, et al. The efficacy of histamine antagonists as antipruritics in experimentally induced pruritis. Arch Dermatol Res 1979;266:117–20.
12. Robertson E, Greaves MW. Responses of human skin blood vessels to synthetic histamine analogues. Br J Clin Pharmacol 1978;5:319–22.
13. Plaut M. Histamine, H_1 and H_2 antihistamines, and immediate hypersensitivity reactions. J Allergy Clin Immunol 1979;63:371–5.

The Effect of Fingerprinting Ink on Pulse Oximetry

To the Editor:

Cote et al. (1) demonstrated that black nail polish may produce factitious decreases in hemoglobin oxygen saturation measured by a pulse oximeter probe applied to the tip of a finger. We have noted that black ink (used to fingerprint mothers after delivery) has a similar effect, as would be expected from its absorption spectrum.

If the oximeter probe is not completely cleaned after fingerprinting, worrisome SaO_2 readings may result.

After we noticed decreased SaO_2 readings (SaO_2 = 93–95%, with an inspired oxygen concentration of 1.0) on several occasions after delivery by cesarean section, differential diagnosis ruled out most causes except amniotic fluid or air embolism. After cleaning the probe light emitter and detector with alcohol wipes and placing the probe on a different finger, the oximeter immediately indicated an SaO_2 of 99–100%. The probe must be placed on a different finger because even after alcohol cleansing, all of the black ink may not be removed from the skin.

Oximeter probes should not be placed on the same fingers that have been fingerprinted. In addition, the probes used during labor and delivery should be cleaned regularly to record accurately.

Michael F. Battito, MD
Department of Anesthesiology
University of Alabama at Birmingham
Birmingham, AL 35233

Reference

1. Cote CJ, Goldstein EA, Fuchsman WH, Hoaglin DC. The effect of nail polish on pulse oximetry. Anesth Analg 1988;67:683–6.

Pulse Oximetry Probe Disconnection

To the Editor:

Pulse oximetry in the operating room and during transportation of the postoperative patient is now recognized as valuable, if not essential, monitoring. Because the pulse

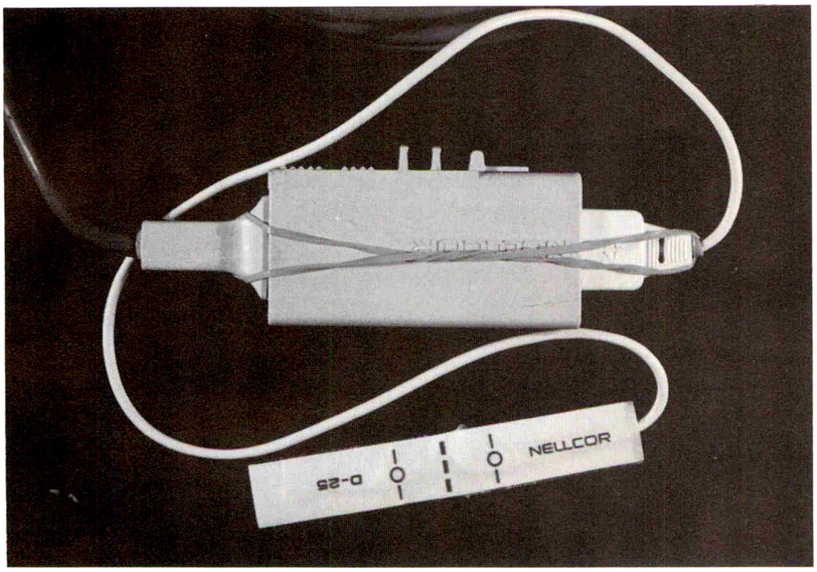


Figure 1. Rubber band placement on pulse oximeter cord and pulse oximeter probe.

oximetry probes are usually placed on the patient's finger or toe, the connection between the pulse oximeter cord and the pulse oximeter probe is often located beneath the surgical drapes and is not visible to the anesthesiologist. Because this is a simple push connection, it is easy for a disconnection to occur as a result of patient movement or the surgeon's manipulation of the surgical drapes.

To circumvent this problem, we have attempted to tape the connection; because of the design of the connecting parts, however, this was not effective in preventing a disconnection. We have found, instead, that a simple rubber band, placed as illustrated in Figure 1, markedly decreases the incidence of pulse oximeter disconnection. This technique, while very simple, improves our ability to monitor patients with the pulse oximeter and results in fewer dives under the drapes to reconnect the cable and probe.

Dennis F. Landers, MD, PhD
Myrna C. Newland, MD
Laurence Wolpert, DO
University of Nebraska Medical Center
42nd and Dewey Avenue
Omaha, NE 68105

An Anesthetic Adapter for All Metered Dose Inhalers that Is Readily Available to All

To the Editor:

Recently, Gold and Marcial (1) reported on a low cost adapter to apply metered dose inhalers (MDIs) to the anesthesia circuit; however, with this technique, either the anesthesia circuit must be disconnected periodically or a piece of custom plasticware, which produces additional deadspace, must be purchased and added to the circuit. We report on an alternative adapter made possible by the advent of sampling analyzers, such as capnographs or mass spectrometers, for which many anesthesia circuits now contain a T-piece adapter. This T-piece usually contains a female Luer-lock side port close to the endotracheal tube, where gas is sampled. This is an ideal location to administer drugs by means of MDIs.

The adapter we devised is inexpensive and easily made and, thus, readily available. A tuberculin syringe is cut at the 0.05-ml mark (approximately 0.33 cm from the neck) after the plunger is removed. When the sampling line has been disconnected, the altered syringe is placed vertically in the Luer-lock opening. This insert narrows the inside diameter of the T-piece enough to allow the MDI to be pressed into position and activated (Fig. 1). With inhalation, single or multiple puffs can be administered easily with the MDI. The plunger from the tuberculin syringe can be used to temporarily plug the adapter. After several breaths are delivered, the adapter is simply removed and the sampling line reconnected.

There are several important considerations when atomized drugs are introduced into an anesthesia circuit by an MDI. First, the patient should be disconnected from the analyzer, mass spectrometer, or capnograph while the drug is administered because the carrier gas in many MDIs causes erroneous mass spectrometry readings (2). Also, such carrier gas could contaminate or occlude the in-line filter of some analyzers. Second, it is easy to keep the MDI canister vertical, which ensures uniform and accurate dosing. Third, agents can easily be given at the beginning of inspiration, as close to the endotracheal tube as possible, to ensure optimal delivery to the lungs. Last, this adapter is easily made from readily available, inexpensive, disposable equipment, and using it does not require glue, additional holes in the circuit, or any other special adjustment.

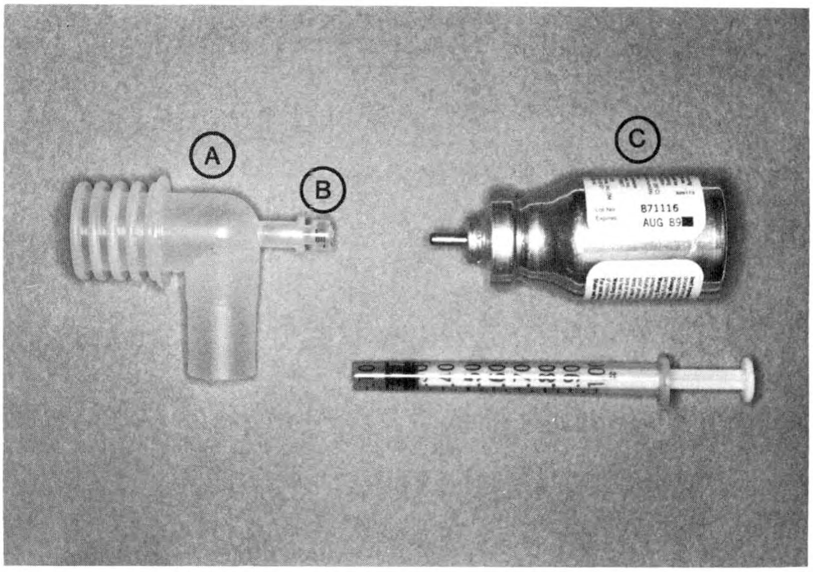


Figure 1. By means of a T-piece adapter **(A)** and a modified tuberculin syringe insert **(B)**, a metered dose inhaler canister **(C)** can be applied to the anesthesia circuit to administer the drug.

Adolph J. Koska III, MD, PhD
David G. Bjoraker, MD
Department of Anesthesiology
University of Florida College of Medicine
Gainesville, FL 32610-0254

References

1. Gold MI, Marcial E. An anesthetic adapter for all metered dose inhalers (letter). Anesthesiology 1988;68:964–6.
2. Theisen GJ, Gravenstein N. More on mass spectrometers and aerosol propellants. Anesthesiology 1985;63:568–9.

Inability to Thread Epidural Catheter through Epidural Needle

To the Editor:

We would like to report a case in which we were unable to pass an epidural catheter through the epidural needle.

After placing the tip of the needle into the lumbar epidural space, using the loss of resistance technique, in a patient about to undergo a cesarean section, we were unable to pass the epidural catheter into the needle provided in our Portex epidural kit. The 19-gauge catheter provided in the kit is designed to pass through the 17-gauge thin-walled epidural needle, also supplied in the kit. The needle was removed from the back and found to be an 18-gauge epidural needle.

Another Portex epidural kit was opened, and the epidural space was relocated using the 17-gauge thin-walled needle. The catheter was passed without difficulty, and the case proceeded without any untoward outcome. Figure 1 shows a photograph of the 17-gauge thin-walled epidural needle placed between the epidural catheter and the 18-gauge needle packaged in the kit.

After discussing this case among the residents, it became apparent that this was not an isolated incident. Two residents reported they had also encountered situations in which they were unable to pass the epidural catheter through the epidural needle. One resident opened another kit, as was done for this patient. The other resident solved the problem by locating a 20-gauge epidural catheter, which he was able to thread through the needle already in place in the patient's epidural space.

We report this incident because it is not a common practice to check the needle and catheter sizes, because the epidural kit is designed with compatible needles and catheters. In addition, it is not recommended to pass the catheter through the needle in advance for fear of shearing the catheter during withdrawal from the needle. We recommend that the imprint on the hub of the needle should be examined to ensure that the needle is the appropriate

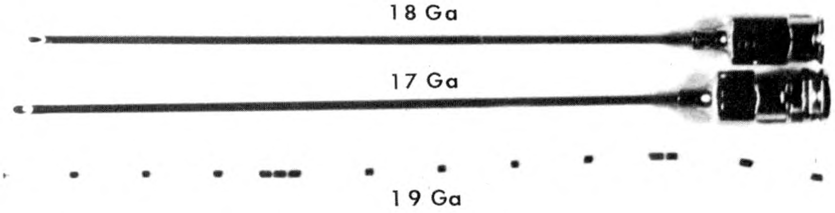


Figure 1. The 17-gauge thin-walled epidural needle between the epidural catheter and the 18-gauge needle packaged in the Portex epidural kit.

size. This should be done before inserting the needle into the back.

David T. Seitman, MD
Bryan E. Shapiro, MD
Department of Anesthesiology
Hahnemann University Hospital
Philadelphia, PA 19102

Aminophylline Reversal of Midazolam Sedation

To the Editor:

Aminophylline has been reported to reverse the sedative effects of diazepam, flurazepam, lorazepam, and flunitrazepam (1–5). The effect on midazolam—a new shorter acting benzodiazepine—has not been reported. The three case reports presented here demonstrate aminophylline can also be used to antagonize the sedative effects of midazolam.

Case 1

A 25-year-old ASA I, 84-kg man underwent incision and drainage of a retromolar abscess under general anesthesia. The only medication he received was 2 mg of midazolam IV 15 min preoperatively and 1 mg of midazolam during the 40-min procedure. He was unable to be aroused at the end of the case and could not maintain his airway. Aminophylline (1 mg/kg) was given IV over 30 sec. The patient became arousable within 1 min and able to maintain his airway. By 2 min he was alert and awake.

Case 2

A 48-year-old ASA 2, 68-kg man underwent lithotripsy for kidney stones. The anesthesia consisted of an epidural with 2% lidocaine. He received a total of 4 mg of midazolam IV over the course of the 1.5-hr procedure. In the recovery room he became somnolent with obstructed breathing. Aminophylline 1 mg/kg was given IV over 30 sec. Within 2 min the patient was awake and alert with an excellent airway.

Case 3

A 25-year-old ASA I, 85-kg man underwent drainage of a peritonsillar abscess. Premedication included midazolam 2.0 mg, fentanyl 25 μg, and glycopyrrolate 0.2 mg IV. Thirty minutes later at the conclusion of the operation he was not arousable. Naloxone (0.4 mg) was given IV with no change over 5 min. Aminophylline (1 mg/kg) was then given IV over 30 sec. The patient became arousable within 2 min and by 3 minutes was awake and talking.

That aminophylline reverses the sedative effects of midazolam is perhaps not surprising given its ability to reverse the effects of other benzodiazepines. However, until specific benzodiazepine antagonists currently being developed are released, it is nice to know that aminophylline is useful in reversing the sedative effects of midazolam, too.

Jonathan S. Gallen, MD
Department of Anesthesiology
Georgia Baptist Medical Center
Atlanta, Georgia

References

1. Stirt JA. Aminophylline is a diazepam antagonist. Anesth Analg 1981; 60:767–8.
2. Phillis JW, Edstrom JP, Ellis SW, Kirkpatrick JR. Theophylline antagonizes flurazepam-induced depression of cerebral cortical neurons. Can J Physiol Pharmacol 1979;57:917–20.
3. Meyer BH, Weis OF, Muller FO. Antagonism of diazepam by aminophylline in healthy volunteers. Anesth Analg 1984;63:900–2.
4. Wangler MA, Kirkpatrick DS. Aminophylline is an antagonist of lorazepam. Anesth Analg 1985;64:834–6.
5. Gurel A, Elevli IM, Hamulu A. Aminophylline reversal of flunitrazepam sedation. Anesth Analg 2987;66:333–6.

Severe Lightning Pain after Spinal Anesthesia in a Patient with Tabes Dorsalis

To the Editor:

We recently observed severe lightning pains postoperatively during spinal anesthesia in a patient who was diagnosed as having tabes dorsalis. A 62-yr-old, 55-kg male was scheduled for surgical repair of the right tibial and fibular fractures. He had previously undergone spinal anesthesia twice, 4 and 5 yr ago, with an uneventful perioperative course. After premedication with 100 mg of intramuscular hydroxyzine and 0.5 mg of atropine sulfate, lumbar puncture was performed at the L4–5 interspace with a 23-gauge needle in the lateral position. Cerebrospinal fluid (CSF) from the needle was clear and 2.2 mL of Neo-Percamin S (combination of 0.24% dibucaine with 0.12% *p*-butylaminobenzol-dietylaminoethanol) was injected over 30 sec. After keeping the patient in the lateral position for 5 min, he was turned to the supine position. Sensory loss measured by pinprick using a 25-gauge needle was at the T-12 dermatomal level 20 min after the intrathecal injection of the solution. On lifting the right leg for sterilizing by the surgeon, the patient complained of severe lightning pains in both legs and buttocks. He started crying in pain, thrashing his arms about, and pounding his head against the pillow. Partial relief of the pain was achieved by the intravenous injection of pentazocine, but the pain completely regressed only 3 hr after the intrathecal injection as the spinal anesthesia wore off.

On physical examination postoperatively, stretch reflexes, especially the Achilles and patellar tendon reflexes were diminished. Argyll Robertson pupils and Romberg's sign were present. The serologic tests for syphilis, including Wassermann test and *Treponema pallidum* hemagglutination assay were also positive. The CSF was not examined.

Tabes dorsalis is a slowly progressive degenerative disease involving the dorsal roots and posterior columns of the spinal cord. Sudden and severe lightning pains involving many organs are a characteristic part of the symptoms. How and why the lightning pains of tabes were triggered by the spinal anesthesia in this patient is not clear but anesthesiologists should be aware of the possibility of such a complication if spinal anesthesia were, despite its being contraindicated, accidentally given to a patient with tabes.

Daisuke Sugiyama, MD, PhD
Katsuya Nobuhara, MD, PhD
Departments of Anesthesia and Orthopedics
Nobuhara Hospital
Hase, Issai, Tatsuno, Hyogo, Japan
Nobuhiro Maekawa, MD, PhD
Hidefumi Obara, MD, PhD
Department of Anesthesiology
Kobe University School of Medicine
Kusunokicho-7, Chuoku, Kobe, Japan

1989;69:270–2

Book Reviews

Cancer Pain

Stephen E. Abram, Boston: Kluwer Academic Publishers, 1989, 173 pp, $69.95.

Pain—unnecessary pain—is the sad fate of most cancer patients; all the sadder because of our own failure to cope adequately with the need for ever larger doses of narcotics, the suffering associated with the diagnosis of cancer, and the emotional impact of disease and pain on patient and family. It is said that up to 85% of terminal cancer patients suffer intolerable pain. Anything we as physicians can contribute to lessen both nociception and terminal suffering will be rewarded by a patient capable of facing certain death with gratitude for not having to suffer needlessly.

This tightly written informative publication in the *Current Management of Pain* series introduces the multidisciplinary approach to management of cancer pain. Dr. Abrams has devoted his life's work to caring for patients in pain, especially patients with cancer pain. This slim volume is a testimonial to his ability to focus interdisciplinary effort on the central problem of cancer pain. Dr. Abram's chapter on nonneurolytic nerve blocks not only is hands-on practical, but also reflects the insight, gained in his years of practice, that nerve block therapy is but a part of total cancer pain management.

The reader is introduced to staged analgesic medication tailored to the patient's increasing needs and progression of disease. Other modalities: surgery, radiation, chemotherapy, electrical stimulation, hormonal therapy, and psychologic and pastoral counseling are nicely integrated into the whole to provide a balanced perspective on a difficult and emotionally laden topic. Missing, regrettably, is a chapter on cancer pain management in children.

I found the chapter on intraspinal narcotics by Coombs particularly effective in teaching pain management, for it speaks not only of successes, but also of failures. We have to accept that "intraspinal" narcotics can not reliably relieve deafferentation pain, and that procedural side effects remain troublesome issues. Neuroablative procedures, whether surgical or neurolytic, do have a unique place in managing intolerable terminal pain. Nevertheless, any irreversible procedure carries with it complications and risks that need to be fully understood by patient and family. Dr. Quimby's chapter on the medicolegal hazards of these procedures points out the need to spend time, use plain words, and document not merely consent, but *fully* informed consent.

In just 170 pages, Dr. Abrams and his contributors have pulled together a well-balanced overview of managing cancer pain. This slender book should be available to house staff, required reading for pain fellows, and be in the personal library of any physician wishing to offer the full range of pain management to patients with cancer pain. While I may not think as much of placebo injections as Dr. Abrams (if it relieves pain, who cares if you used saline or lidocaine?), I found the book a sobering guide in working with cancer patients, a comfort in communicating with oncology colleagues, and an excellent introduction to the interdisciplinary approach for house staff and students rotating through the pain service.

Rudolph H. de Jong, MD
Department of Anesthesiology and Psychiatry
Interdisciplinary Pain Management Center
Medical College of Georgia
Augusta, Ga

Anesthesia and the Heart Patient

Fawzy G. Estafanous, ed. Boston: Butterworths, 1989, 367 pp, $65.00.

This volume, an outgrowth of the second international symposium "Anesthesia and the Heart Patient" held in November 1986, consists of 42 chapters contributed by 51 authors, of whom 14 are staff members of the sponsoring institution, the Cleveland Clinic. The preface states that it is "not a general textbook... but rather a forum for the presentation and exchange of the latest knowledge, clinical experiences, and patient management practices of distinguished experts from leading centers around the world." Indeed, many of the best-recognized clinicians and investigators in cardiac anesthesia today are among the authors.

The book has the expected chapters covering use in the cardiac patient of inhalation anesthetics, benzodiazepines, opiates, muscle relaxants, antiarrhythmics, inotropes, vasodilators, and adjuvant drugs. The chapters on managing specific disease entities emphasize facets of coronary artery disease, including catheterization, thrombolytic therapy, angioplasty, coronary artery bypass, ventricular mapping, and ventricular aneurysmectomy. There are also excellent chapters on congenital heart surgery, cardiac transplanta-

©1989 by the International Anesthesia Research Society

tion, aortic aneurysmectomy, carotid endarterectomy, and major vascular and thoracic surgery. Some general topics pertaining to cardiac surgery are given more detailed treatment than they are in conventional textbooks, including myocardial protection, heparin and protamine effects, blood conservation, reoperative surgery, myocardial failure, mechanical assist devices, monitoring, and selected postoperative problems.

A major strength is that the book provides insights and practical recommendations derived from the vast institutional and individual experience of many of the authors. Another strength is the perspective added by the 13 surgeons, cardiologists, and other nonanesthesiologist authors. I was disappointed not to see more space devoted to valvular surgery, pacemakers, implanted cardioverter/defibrillators, and intraoperative echocardiography.

The book is only slightly marred by the usual shortcomings of multiauthorship—repetition and uneven style and quality of the chapters. The editing and production is generally good, although I found a few glaring errors of substance. The material is fairly up-to-date, with some chapters having references as recent as 1988. The 1989 copyright date is misleading, however, as I received the review copy in November 1988.

This book fills an important gap between cardiac anesthesia textbooks and the relevant journal articles widely scattered in the anesthesiology, cardiology, cardiac surgery, and pharmacology literature. It would be a useful addition to the library of any hospital where major cardiovascular surgery is performed. It should be "must" reading for those doing fellowship training in cardiac anesthesia, because it goes beyond the textbooks in providing in-depth coverage and practical guidelines about some of the major problems facing the subspecialty. To the budding clinical investigator it may also suggest directions for research, and it would be a most useful refresher for the experienced practitioner.

G. Bashein, MD, PhD
Department of Anesthesiology
University of Washington
Seattle, Wash

Clinical Anatomy for Anesthesiologists

Richard S. Snell and Jordan Katz. East Norwalk, CT: Appleton and Lange, 1988, 328 pp, $95.00.

This book is intended to provide the anesthesiologist with the basic knowledge of anatomy necessary for practicing anesthesiology. The scope of the book has been limited by including only selected organ systems and subunits of the body. To adopt this approach requires a judgment as to what is the more important material to include. The authors have included nine chapters: two on the respiratory system (61 pages), one on the cardiovascular system (56 pages), one on the vertebral column (34 pages), four on the nervous system (134 pages), and one covering reception of pain and control of muscular activity (26 pages).

The chapters are well illustrated. Most commonly the illustrations are black and white line drawings, but in every chapter color has been used successfully in certain of the drawings to enhance points being made. There are also photographs, radiographs, photomicrographs, and computed tomography scans. The authors clearly have insight into anesthesia practice, in that, in many instances they have selected illustrations that cover areas of anatomy that practitioners as well as physicians-in-training find perplexing.

Even though the scope of the book has been limited by including chapters only on certain systems, within some of the areas included the authors still appear to have had difficulty in deciding what to exclude. This apparent dilemma appears to have been handled by including many topics but making the description short and very terse. This is particularly true in the chapter on the autonomic nervous system. In some instances a knowledge beyond what most practitioners and students of anesthesiology may have is required to follow and understand the terse descriptions provided.

The goal of the authors to emphasize the practical application of anatomical facts to anesthesiology has been achieved to a limited extent; one would hope later editions will add even more practical applications. At the end of each chapter there are two to four pages of clinical notes followed by 10–12 clinical problems (usually brief case histories) and the anatomical explanation relating to the clinical findings. Many of these are directed at what appears to be a basic level rather than at the level of the practicing anesthesiologist.

The inclusion of a separate chapter on the autonomic nervous system is an excellent idea and reflects that the authors appreciate the difficulty of this system and the need anesthesiologists have in understanding it. The brevity of the coverage of some areas and the writing style selected may limit the usefulness of this chapter. The writing style which uses the verb "give" or "join" (e.g., page 263 and elsewhere to describe the origin and/or course of nerve branches) makes understanding more difficult, particularly when the order of anatomical structures given in the sentence is opposite to the direction in which impulses pass in the nerves.

The book contains a wealth of information. It is more likely to be found useful by anesthesiologists needing a refresher course than by students or residents.

Duane K. Rorie, MD, PhD
Department of Anesthesiology
Mayo Clinic and Mayo Foundation
Rochester, Minn

Anatomy for Anaesthetists (fifth edition)

Harold Ellis and Stanley Feldman. Boston: Blackwell Scientific Publications, 1988, 376 pp, $75.00.

This text was written originally to help prepare candidates taking the primary FFARCS when anatomy was one of the three principal subjects. The thrust of the current edition is to attempt to provide the detailed anatomical knowledge that anesthetists need as a background to their daily work. To accomplish this goal, the entire text has been revised and a number of the 217 figures revised. Most of the figures are black and white line drawings, but some have color features to emphasize specific points. The drawings are well labeled and are effective in helping readers grasp the points being made.

To accomplish their goals, the authors have covered the respiratory system, heart, and peripheral nerves in considerable detail. The section on peripheral nerves contains chapters on the autonomic nervous system and the anatomy of pain. A section covering the vertebral canal and its contents is also included.

The book has an interesting section at the end called "Zones of Anesthetic Interest." This section contains information on a multitude of topics of interest to anesthesiologists, several of which relate anatomy to many of the technical procedures anesthesiologists perform. While this section contains an abundance of practical anatomy, practical applications of anatomy are not limited to this section but rather are interspersed throughout all of the chapters.

A strong point of this book is the excellent style in which it is written; it flows well and is very easy to read. The anesthesiologist educated in the United States will, however, occasionally find unfamiliar anatomical terminology. While this may serve to broaden one's knowledge, the use of the term "theca" to refer to the brachial plexus sheath was sufficiently different that it served to slow my reading pace. Overall, I did not find the difference in terminology a major problem.

Duane K. Rorie, MD, PhD
Department of Anesthesiology
Mayo Clinic and Mayo Foundation,
Rochester, Minn

The Anesthesiology Boards Review Course

*September 4-9, 1989 — Ft. Lauderdale
*April 16-21, 1990 — Dallas

Now, your only broad review just before Written and Oral Exams
Participants rate this course better than any they have attended

OBJECTIVES

- Improve basic and clinical knowledge in anesthesiology
- Assist residents and fellows in organizing study
- Prepare candidates to take examinations
- Provide practicing anesthesiologists with a review and update

METHODS

- HOME STUDY MATERIALS consisting of a syllabus of questions with assignments and answers
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

* Sept. 4-9 (live) and Sept. 10-13 (video replays) and Sept. 10-11 (optional extra mock oral exams); similar additions in April 1990

---

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

PHYSIOLOGY
- Respiratory Physiology
- Cardiovascular Physiology
- Neurophysiology
- Hepatic Physiology
- Renal Physiology
- Acid-Base and Blood Gas
- Endocrine Physiology
- Thermoregulation

PHARMACOLOGY
- Pharmacokinetics
- Inhalation Anesthetics
- Intravenous Anesthetics
- Muscle Relaxants
- Autonomic Drugs
- Central Nervous Drugs
- Cardiac & Diuretic Drugs
- Interactions & Genetics

PHYSICAL SCIENCES
- Applied Anatomy
- Physics and Gas Laws
- Anesthesia Machines
- Instrumentation
- lonitors and Ventilators
- eathing Systems
- efibrillators and Pacers

FUNDAMENTALS
- Preop. Evaluation & Prep.
- Patient Monitoring
- Airway Management
- Fluid and Blood Therapy
- Cardiopulmonary Disease
- Hepatic & Renal Disease
- Metabolic Disease
- Recovery Room

REGIONAL ANESTHESIA
- Local Anesthetics
- Autonomic Blocks
- Spinal and Epidural Blocks
- Caudal Blocks
- Upper Extremity Blocks
- Lower Extremity Blocks
- Chronic Pain Management

SPECIALTY AREAS
- Obstetric Anesthesia
- Pediatric Anesthesia
- Cardiac Anesthesia
- Thoracic Anesthesia
- Neuroanesthesia
- Opthalmic & E.N.T.
- Geriatric and Outpatients
- Critical Care

Ezzat Abouleish, M.D.
University of Texas at Houston
Soloman Aronson, M.D.
University of Chicago
Jonathan Benumof, M.D.
University of California at San Diego
George Bikhaze, M.D.
University of Miami
T. Andrew Bowdle, M.D., Ph.D.
University of Washington
Eugene Y. Cheng, M.D.
Medical College of Wisconsin
Hernando DeSoto, M.D.
Riverside Hosp., Jacksonville, FL
Elizabeth Frost, M.D.
Albert Einstein College of Medicine
Allen Hord, M.D.
Emory University
Joseph Johnston, M.D.
Medical College of Georgia
Terence Murphy, M.D.
University of Washington
Nathan Pace, M.D.
University of Utah
Danae Powers, M.D.
Emory University
Michael Ritter, M.D.
Emory University
Bruce Schreider, M.D., Ph.D.
University of Chicago
Daniel Siker, M.D.
Medical College of Wisconsin
Theodore Smith, M.D.
Loyola University of Chicago
Albert Varnon, M.D.
University of Miami
Marcelle Willock, M.D.
Boston University
Kenneth Zahl, M.D.
Mount Sinai School of Medicine

Limited Enrollment: ANESTHESIOLOGY COURSE REVIEW REGISTRATION

Name ______________________________

Address ______________________________

City/State/Zip ______________________________

Phone ____________________

For: ☐ Sept. 4-9, '89 — Ft. Lauderdale
☐ April 16-21, 1990 — Dallas
☐ July 7-12, 1990 — Chicago

☐ Check enclosed for $ __________

☐ Please send more information

Mail today to:

1094 Dawn Lane, Dept. AA8
P.O. Box 2218
Terre Haute, IN 47802

---

*"Accommodations were comfortable...."**

GOALS AND LOCATION: This course is to help you pass your board exams. It is held the week before and in the same city as oral boards and also in Chicago the week before written exams. You will receive home study material upon registration. Your best value is to repeat the course for half price the week before both written and oral exams. In Ft. Lauderdale it will be at the Sheraton Bonaventure - a world class conference center and resort — $92 Single; $112 double. Breakfast, lunch and breaks are included.

*"...and those little extras...."**

LOWEST AIR FARES: Please call toll-free 1-800-843-1220 and identify yourself with this Osler course.

*"...remarkably complete and pleasant."**

PLACEMENT SERVICE: For practice opportunities write or call 1-800-356-7537.

*"...the most education for the money."**

FEES AND C.M.E. CREDITS:

Continuing Medical Education	**60 hours**
Practicing Anesthesiologists:	$660
Residents and Fellows:	$440
Repeating course within 3 years:	half price
Extra Practice Orals (Sept. 10-12)	$120/day

- **Add 10% within 10 days of the course.**
- Attendees not in course hotel add $60.
- Deposit of $50 will reserve your position.
- Most home study materials will be mailed after half the registration fee is received.

*"...home study material was extremely helpful."**

REFUNDS: Subject to $50 fee, refunds will be made until the seminar begins.
- Cancellation after mailing home study material requires retention of half of the fee.

*"I feel [the course] helped me pass ...."**

INFORMATION:
Joseph H. Selliken, Jr., M.D.
THE OSLER INSTITUTE
1094 Dawn Lane, P.O. Box 2218
Terre Haute, IN 47802
(800) 356-7537 or (812) 299-5658

* *Comments by past Osler participants*

The first preservative-free morphine sulfate worthy of sharing the Astra name

Astramorph™ PF Ⓒ II
(morphine sulfate injection, USP)

- 9 JAN 1990

NTRA

- Preservative-free solutions
- 0.5 mg/mL and 1 mg/mL dosage forms
- 10 mL E-Z OFF™ vials—also 2-mL and 10-mL ampules
- Intrathecal dosage form—1-mg, 2-mL ampule
- Tamper-evident "porthole" packaging
- Proven, reliable Astra quality

The name says it all

ASTRA® | Astra Pharmaceutical Products, Inc.
Westborough, MA 01581

© Astra 1989

AST 19201